90 Rec'd PCT/PTO 03 MAY 2001

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
206523US0PCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
09/807990

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/05973	**1 September 2000**	**3 September 1999**

TITLE OF INVENTION
MUTANT NUCLEOSIDE-5'-PHOSPHATE PRODUCING ENZYMES

APPLICANT(S) FOR DO/EO/US
Kohki ISHIKAWA, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

PCT/IB/304 **Notice of Priority**
PCT/IB/308 **Sequence Listing (44 Pages)**
Drawings (47 Sheets)
Request for Consideration of Documents Cited in International Search Report

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U.S. APPL. NO.	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/807990	PCT/JP00/05973	206523US0PCT

24. The following fees are submitted:.

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	27 - 20 =	7	x $18.00	**$126.00**	
Independent claims	16 - 3 =	13	x $80.00	**$1,040.00**	
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$2,026.00**	
☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**	
SUBTOTAL =				**$2,026.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$2,026.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$2,026.00**	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$2,026.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. ______________ in the amount of ______________ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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REGISTRATION NUMBER

May 3 2001
DATE

#5/B

Docket No.: 206523US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: : ATTN: BOX SEQUENCE

KOHKI ISHIKAWA ET AL :

SERIAL NO.: 09/807,990 :

FILED: MAY 3, 2001 :

FOR: MUTANT NUCLEOSIDE-5'-PHOSPHATE PRODUCING ENZYMES

PRELIMINARY AMENDMENT AND STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Responsive to the Office Communication mailed June 12, 2001, please amend the above-identified application as follows:

IN THE SPECIFICATION

Please delete the original Sequence Listing.

Page 94 (Abstract), after the last line, beginning on a new page, please insert the attached substitute Sequence Listing.

REMARKS

Claims 1 - 27 are pending in the present application.

Applicants have now submitted a substitute Sequence Listing and a corresponding computer-readable Sequence Listing. The sequence information recorded in the

corresponding computer-readable Sequence Listing is identical to the paper copy of the substitute Sequence Listing. Support for all of the sequences listed in the substitute Sequence Listing is found in the present application as originally filed. No new matter is believed to have been introduced by the submission of the substitute Sequence Listing and the corresponding computer-readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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206523US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

KOHKI ISHIKAWA ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW US PCT APPLN. :
(Based on PCT/JP00/05973)

FILED: HEREWITH :

FOR: MUTANT NUCLEOSIDE-5'-PHOSPHATE PRODUCING ENZYMES :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown in the marked-up copy to read as follows.

23. (Amended) A gene coding for any one of the enzymes according to claim 1.

25. (Amended) A microorganism, which contains the gene according to claim 23.

26. (Amended) A method for producing a nucleoside-5'-phosphate, which comprises allowing the enzyme according to claim 1 to act on a nucleoside and a phosphate donor to produce nucleoside-5'-phosphate and collecting it.

27. (Amended) The method according to claim 26, wherein the enzyme is allowed to act on a nucleoside and a phosphate donor under a condition of pH 3.0-5.5.

REMARKS

Claims 1-27 are active in the present application. The claims are amended to remove multiple dependencies. No new matter is added. An action on the merits and allowance of the claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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Marked-Up Copy
Serial No:

Amendment Filed on:

IN THE CLAIMS

Please amend the claims as follows.

--23. (Amended) A gene coding for any one of the enzymes according to [any one of claims 1-16] claim 1.

25. (Amended) A microorganism, which contains the gene according to claim 23 [or the recombinant DNA according to claim 24].

26. (Amended) A method for producing a nucleoside-5'-phosphate, which comprises allowing the enzyme according to [any one of claims 1-16, a microorganism containing it or the microorganism according to claim 25] claim 1 to act on a nucleoside and a phosphate donor to produce nucleoside-5'-phosphate and collecting it.

27. (Amended) The method according to claim 26, wherein the enzyme[, the microorganism containing it or the microorganism according to claim 25] is allowed to act on a nucleoside and a phosphate donor under a condition of pH 3.0-5.5.--

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SPECIFICATION

Mutant nucleoside-5'-phosphate producing enzymes

Technical Field

The present invention relates to mutant nucleoside-5'-phosphate producing enzymes with improved nucleoside-5'-phosphate producing ability, and a method for producing them. The present invention further relates to enzymes useful for the production of the aforementioned enzymes. Furthermore, the present invention relates to methods for producing a nucleoside-5'-phosphate as well as genes coding for the aforementioned mutant enzymes, recombinant DNA containing the genes and microorganisms that harbor the recombinant DNA, which are useful for the production methods. Nucleoside-5'-phosphates are useful as seasonings, drugs, raw materials therefor and so forth. The present invention is based on successful elucidation of the three-dimensional structures of a novel protein, and the three-dimensional structures have expandability that they are not limited to microorganisms.

Background Art

As a method for efficiently producing nucleoside-5'-phosphates at a low cost by biochemically phosphorylating nucleosides, there was developed a

method of efficiently producing a nucleoside-5′-phosphate without generation of byproducts of nucleoside-2′-phosphate acid and nucleoside-3′-phosphate isomers, which comprises allowing cells of a particular microorganism to act on a nucleoside and a phosphate donor selected from the group consisting of polyphosphoric acid (salt thereof), phenyl phosphate (salt thereof) and carbamyl phosphate under an acidic condition (Japanese Patent Laid-open (Kokai) No. 7-231793/1995).

Then, it was confirmed that the productivity of nucleoside-5′-phosphates can further be improved by obtaining a gene coding for an acid phosphatase from *Escherichia blattae* or *Morganella morganii* and expressing the gene in *Escherichia coli* in a large scale using genetic engineering techniques.

The structure of the acid phosphatase is shown in Fig. 2. That is, Fig. 2 shows alignment of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* (abbreviated as "EB-AP" hereinafter) with the amino acid sequences of acid phosphatases derived from *Morganella morganii*, *Salmonella typhimurium* and *Zymomonas mobilis*. The asterisks indicate conserved residues. The regions of the secondary structure are indicated with bars over the aligned sequences. The boxed portions are motives commonly observed in the acid phosphatase family. The motives consist of three

domains, 1) KXXXXXXRP (SEQ ID NO: 121), 2) PSGH (SEQ ID NO: 122) and 3) SRXXXXXHXXXD (SEQ ID NO: 123). In these motives, X represents an arbitrary amino acid residue.

Although these acid phosphatases (Fig. 2) have transphosphorylation activity, they suffer from a drawback that their phosphatase activity for decomposing nucleoside-5′-phosphate into a nucleoside is dominant in wild-type strains, and hence accumulated nucleoside-5′-phosphate will be decomposed. Therefore, a large number of mutant enzymes were generated by the random mutagenesis method, and a mutant acid phosphatase having relatively improved transphosphorylation activity compared with phosphatase activity was found among the mutant enzymes. And it was demonstrated that the productivity of nucleoside-5′-phosphate was drastically improved by abundantly expressing a gene coding for the mutant acid phosphatase gene (Japanese Patent Laid-open (Kokai) No. 8-535568/1996).

This mutant acid phosphatase has improved affinity for a nucleoside, and it is thought that the transphosphorylation activity was improved by the enhanced affinity.

It was demonstrated that the aforementioned mutant acid phosphatase derived from *Escherichia blattae* (=G74D/I153T mutant enzyme (mutant enzyme in which 74th Gly is replaced with Asp and 153rd Ile is replaced with Thr, the mutation pattern will be similarly represented

hereinafter)) showed weaker transphosphorylation activity compared with a corresponding G72D/I151T mutant enzyme of acid phosphatase derived from *Morganella morganii* (MM-AP), whereas a 10-residue replaced L63Q/A65Q/E66A/N69D/S71A/S72A/G74D/T135K/E136D/I153T mutant enzyme (referred to simply as "10-residue replaced mutant EB-AP" hereinafter), in which 8 amino acid residues were replaced with the amino acids of MM-AP that correspond on the primary structure basis, showed transphosphorylation activity substantially comparable to that of G72D/I151T mutant MM-AP (Japanese Patent Laid-open (Kokai) No. 9-161674/1997).

A method for producing a nucleoside-5'-phosphate has been established by expressing a large amount of the aforementioned G74D/I153T mutant enzyme gene ~~for acid phosphatase with improved productivity derived from *Escherichia blattae* (EB-AP)~~, or the 10-residue replaced mutant enzyme gene in *Escherichia coli* (Japanese Patent Laid-open (Kokai) Nos. 9-37785/1997 and 10-201481/1999). However, a mutant EB-AP with further improved productivity is still desired.

Disclosure of the Invention

The object of the present invention is to further improve the productivity of nucleoside-5'-phosphate by designing a mutant EB-AP based on the three-dimensional structure of EB-AP.

That is, aspects of the present invention are as follows:

(1) A mutant nucleoside-5′-phosphate producing enzyme with improved nucleoside-5′-phosphate producing ability, which is obtained by modifying a nucleoside-5′-phosphate producing enzyme that has transphosphorylation activity and/or phosphatase activity and has one Lys residue, two Arg residues and two His residues with distances between their Cα's within the ranges shown in Fig. 1 and a space around them allowing a binding of a nucleoside.

(2) The mutant nucleoside-5′-phosphate producing enzyme according to (1), wherein the distances between Cα's of the Lys residue, two Arg residues and two His residues are within the ranges shown in Fig. 1.

(3) The mutant nucleoside-5′-phosphate producing enzyme according to (1), wherein the nucleoside-5′-phosphate producing ability is improved by predicting a binding mode of the enzyme to a nucleoside such as inosine and guanosine and phosphorylated compounds thereof based on the atomic coordinate data obtained by X-ray crystallographic analysis of acid phosphatase derived from *Escherichia blattae*, and substituting, adding or deleting at least one amino acid residue and/or a prosthetic factor etc.

(4) The mutant nucleoside-5′-phosphate producing enzyme according to (1), wherein the enzyme is derived

from a bacterium belonging to the genus *Escherichia*, *Morganella*, *Providencia*, *Enterobacter* or *Klebsiella*.

(5) A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has an amino acid sequence of the acid phosphatase derived from *Escherichia blattae* including modification at one or more of the following positions (Ser72~~ of *Escherichia blattae* acid phosphatase~~ or residues located within a distance of 10Å from Ser72): 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 149-154, 157, 179 and 183.

(6) A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions in the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* (Ser72 of *Escherichia blattae* acid phosphatase or residues located within a distance of 10Å from Ser72): 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 149-154, 157, 179 and 183 in amino acid sequence alignment with the acid phosphatase derived from *Escherichia blattae*.

(7) A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or

more of positions corresponding to the following positions in the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* (Ser72 of *Escherichia blattae* acid phosphatase or residues located within a distance of 10Å from Ser72): 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 149-154, 157, 179 and 183 in alignment with the three-dimensional structure of the acid phosphatase derived from *Escherichia blattae* performed by the threading method.

(8) The mutant nucleoside-5'-phosphate producing enzyme according to (6), wherein the three-dimensional structure of the enzyme is put close to that of an enzyme derived from another organism having transphosphorylation activity higher than that of a wild-type of the enzyme having the transphosphorylation activity and/or phosphatase activity by making modification at one or more positions other than the positions (Ser72 of *Escherichia blattae* acid phosphatase or residues present within a distance of 10Å from Ser72).

(9) A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has an amino acid sequence of the acid phosphatase derived from *Escherichia blattae* including modification at one or more of the following positions: 16, 71, 72, 73, 103, 104, 140, 151 and 153.

(10) A mutant nucleoside-5'-phosphate producing

enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae*: 16, 71, 72, 73, 103, 104, 140, 151 and 153 in amino acid sequence alignment with the acid phosphatase derived from *Escherichia blattae*.

(11) A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae*: 16, 71, 72, 73, 103, 104, 140, 151 and 153 in alignment with the three-dimensional structure of the acid phosphatase derived from *Escherichia blattae* performed by the threading method.

(12) A mutant nucleoside-5'-phosphate producing enzyme, which has an amino acid sequence of the acid phosphatase derived from *Escherichia blattae* including replacement of the 72nd residue with another amino acid residue.

(13) A mutant nucleoside-5'-phosphate producing enzyme, which has transphosphorylation activity and/or

phosphatase activity, and has replacement of a residue corresponding to the 72nd residue of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* with another amino acid in amino acid sequence alignment with the acid phosphatase derived from *Escherichia blattae*.

(14) A mutant nucleoside-5′-phosphate producing enzyme, which has transphosphorylation activity and/or phosphatase activity, and has replacement of a residue corresponding to the 72nd residue of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* with another amino acid in alignment with the three-dimensional structure of the acid phosphatase derived from *Escherichia blattae* performed by the threading method.

(15) The mutant nucleoside-5′-phosphate producing enzyme according to (10), wherein the enzyme is derived from *Enterobacter aerogenes*, and the amino acid sequence of the enzyme includes replacement with another amino acid residue of at least one amino acid residue among the 14th leucine residue, the 61st leucine residue, the 63rd alanine residue, the 64th glutamic acid residue, the 67th asparagine residue, the 69th serine residue, the 70th alanine residue, the 71st glycine residue, the 72nd glycine residue, the 101st isoleucine residue, the 102nd glutamic acid residue, the 133rd threonine residue, the 134th glutamic acid residue, the 138th leucine

residue, 149th threonine residue and the 151st isoleucine residue.

(16) The mutant nucleoside-5′-phosphate producing enzyme according to (12), wherein the enzyme is derived from *Enterobacter aerogenes*, and the enzyme has any one of following amino acid replacements:

(a) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a valine residue, the 72nd glycine residue with an aspartic acid residue, the 102nd glutamic acid residue with a leucine residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a serine residue and the 151st isoleucine residue with a serine residue;

(b) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a valine residue, the 72nd glycine residue with an aspartic acid residue, the 133rd

threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a alanine residue and the 151st isoleucine residue with a serine residue;

(c) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a glutamic acid residue, the 72nd glycine residue with an aspartic acid residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a glycine residue and the 151st isoleucine residue with a serine residue;

(d) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a lysine residue, the 72nd glycine residue with an aspartic acid residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a glycine residue and the

151st isoleucine residue with a serine residue; and

(e) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a methionine residue, the 72nd glycine residue with an aspartic acid residue, the 102nd glutamic acid residue with a glutamine residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a serine residue and the 151st isoleucine residue with a serine residue.

(17) A method for producing a mutant nucleoside-5'-phosphate producing enzyme, wherein a mutant enzyme with improved nucleoside-5'-phosphate producing ability is produced by substituting, adding or deleting at least one amino acid residue in the active site of an enzyme having transphosphorylation activity and/or phosphatase activity and/or an amino acid residue located within a distance of 10Å from the active site, in which the active site is determined based on the three-dimensional structure of the enzyme obtained by X-ray crystallographic analysis of the enzyme or a complex of the enzyme with molybdate.

(18) A method for producing an inhibitor for a

phosphatase or transphosphorylation enzyme, which utilizes the atomic coordinates of the acid phosphatase derived from *Escherichia blattae*.

(19) A crystal of an enzyme having transphosphorylation activity and/or phosphatase activity or the complex of the enzyme with molybdate.

(20) A crystal of acid phosphatase derived from *Escherichia blattae*, which has a space group $P6_322$ of a hexagonal system.

(21) A crystal of mutant enzyme acid phosphatase G74D/I153T derived from *Escherichia blattae*, which has a space group $P2_12_12_1$ of a rhombic system.

(22) A crystal of complex of acid phosphatase derived from *Escherichia blattae* and molybdate (reaction intermediate analogue), which has a space group $P3_121$ of a trigonal system.

(23) A gene coding for any one of the enzymes according to any one of (1) to (16).

(24) A recombinant DNA, which contains the gene according to (23).

(25) A microorganism, which contains the gene according to (23) or the recombinant DNA according to (24).

(26) A method for producing a nucleoside-5'-phosphate, which comprises allowing the enzyme according to any one of (1) to (16), a microorganism containing it or the microorganism according to (25) to act on a

nucleoside and a phosphate donor to produce nucleoside-5'-phosphate and collecting it.

(27) The method according to (26), wherein the enzyme, the microorganism containing it or the microorganism according to (25) is allowed to act on a nucleoside and a phosphate donor under a condition of pH 3.0-5.5.

The present invention provides a method for producing nucleoside-5'-phosphate using a mutant EB-AP, which is designed based on a binding model of EB-AP with a nucleoside constructed on the basis of the three-dimensional structure of EB-AP.

However, the mutant nucleoside-5'-phosphate producing enzyme of the present invention does not include the G74D/I153T mutant EB-AP, the G72D/I151T mutant MM-AP and the 10-residue replaced mutant EB-AP.

The present invention will be specifically explained hereinafter.

(1) In order to determine the three-dimensional structure of a protein by X-ray crystallography, the protein must be crystallized (details will be described in Examples 1-3). In order to crystallize a protein, many parameters must be determined on the trial and error basis, such as pH, kind of buffer, concentration of buffer, kind of precipitating agent, concentration of

precipitating agent, concentrations of additives such as metals, concentration of protein and purity of protein. Therefore, it usually takes ~~time of~~ several months to several years before obtaining crystals, and there is often a case where crystals cannot be obtained in spite of such great effort. While crystallization is indispensable for the determination of the three-dimensional structure, it is also industrially useful as purification method of proteins to high purity, method for storage of proteins with high density and high protease resistance as well as a process prior to utilization as immobilized enzymes.

(2) By irradiating the produced crystals with an X-ray, diffraction data are collected. A protein crystal is often damaged by X-ray irradiation, and thus suffers from degradation of diffraction ability. For such a case, low temperature measurement recently becomes popular, in which crystals are rapidly cooled to about −173°C and diffraction data are collected in that state. Upon cooling, it is necessary to devise a solvent composition so that the crystals should not be destroyed and the whole system should be vitrified.

(3) In order to perform crystal structure analysis, phase information is required in addition to the diffraction data.

Since three-dimensional structures of proteins analogous to EB-AP have not been known yet, the problem concerning the phase must be solved by the heavy atom isomorphous replacement method. The heavy atom isomorphous replacement method is a method for obtaining phase information by introducing a metal of a large atomic number such as mercury and platinum into a crystal and utilizing contribution of strong X-ray scattering ability of metal atoms to X-ray diffraction data to obtain phase information. If the three-dimensional structure of wild-type EB-AP is once determined, crystal structures of analogous compounds thereof such as mutant enzymes and reaction intermediate analogues can be determined by the molecule replacement method by using it. The molecule replacement method is a technique for crystal structure determination by using a three-dimensional structure of a protein analogous to the protein of which crystal structure is to be determined, when the three-dimensional structure of the analogous protein is known. For example, if a three-dimensional structure of a wild-type of a certain protein is known, the molecule replacement method can be used for the determination of a crystal structure of a mutant protein or a chemically modified protein thereof.

As for the G74D/I153T mutant EB-AP, its crystal structure is determined for elucidating the molecular mechanism for the enhancement of affinity for a

nucleoside by substitution of two amino acids.

As for a reaction intermediate analogue, its crystal structure is determined in order to construct its binding model with a nucleoside. A nucleoside binds to EB-AP to which phosphate group to be donated binds through a covalent bond, i.e., a reaction intermediate, and then converted into a nucleoside-5′-phosphate. Since the reaction intermediate of EB-AP is unstable, its structure cannot be determined. It was considered that, however, since a reaction intermediate analogue to which molybdate binds through a covalent bond instead of phosphate was not hydrolyzed, its structure could be determined. The details will be described in Examples 4, 6, and 7.

(4) On computer graphics (CG), a binding mode model is constructed by fitting a nucleoside to a hollow near the molybdate binding site ~~based on the binding site~~ in the three-dimensional structure of the reaction intermediate analogue (Fig. 3). For the construction of the model, a program such as QUANTA and INSIGHT II of MSI (United States) is utilized.

Fig. 3 is a photograph of the crystal structure of the aforementioned binding mode model.

The details will be described in Examples 5 and 8.

(5) By extensively examining the binding model, a

mutation that is considered to increase the affinity for a nucleoside is designed. In order to improve the affinity, it is effective to enhance hydrophobic interaction, electrostatic interaction, hydrogen bond, π-π interaction (interaction of magnetic fields generated by ring currents of aromatic rings) and CH/π interaction (interaction of magnetic field generated by ring current of an aromatic ring and electrons of methyl group).

For example, since it is expected that Ser72 most strongly interacts with a base of nucleoside in the binding mode model, it can be considered that replacement of the residue with Phe, Tyr and Trp enhances the hydrophobic interaction and the π-π interaction, replacement with Val, Ile and Leu enhances the hydrophobic interaction and the CH/π interaction, and replacement with Glu and Asp enhances the electrostatic interaction and the hydrogen bond. Further, the hydrophobic interaction and so forth may also be enhanced by replacement with other amino acids, in particular, replacement with an amino acid having a longer side chain.

It is also expected that replacements of Leu16, Ser71, Ser73 and Glu104 with Phe, Tyr and Trp generate the π-π interaction between the aromatic rings of the replaced amino acid residues and a base of nucleoside. Further, it is expected that replacements of Ile103 or

Thr153 with a hydrophilic residue having a longer chain generate a hydrogen bond with the ribose of nucleoside. Furthermore, it is expected that replacement of Thr151 that is present near the nucleoside binding site and buried inside the protein with an amino acid residue having a small side chain such as Ser, Ala and Gly produces a space in the protein so that flexibility of the nucleoside binding site is increased and the binding site can have a conformation more suitable for binding with a nucleoside. Although Leu140 is separated from Ser72 by more than 10Å, it is located near the phosphate binding site in the three-dimensional structure of a reaction intermediate analogue. Therefore, it is considered that if this residue is replaced, the structure around the phosphate binding site of the reaction intermediate is changed, and as a result, it also influences the structure of the nucleoside binding site and fluctuation thereof. It is expected that if this residue is replaced with more bulky Phe, positively charged Lys or negatively charged Glu, the affinity with a nucleoside may be changed.

The aforementioned mutations are introduced into, for example, the G74D/I153T mutant EB-AP. However, the mutant enzyme to which the mutations are introduced is not limited to the G74D/I153T mutant EB-AP. For example, it is also possible to introduce the mutations into the 10-residue replaced mutant EB-AP.

The details will be described in Example 10.

(6) A plasmid containing a gene coding for a mutant EB-AP is produced. The gene coding for a mutant EB-AP can be obtained by introducing a target mutation into a gene coding for a wild-type EB-AP through site-specific mutagenesis.

The plasmid containing the gene coding for a mutant EB-AP is introduced into *Escherichia coli* JM109 to produce a mutant EB-AP. A Km value, which serves as an index of affinity of the mutant EB-AP for inosine, and transphosphorylation activity to convert inosine into 5′-inosinic acid are measured to evaluate the performance of the mutant EB-AP. It is considered that the production amount of nucleoside-5′-phosphate much depends on the Km value. After pyrophosphoric acid reacts with EB-AP and a phosphate ion dissociates so that a reaction intermediate with the phosphate group covalently bonded to EB-AP is formed, if a water molecule attacks it, the phosphate group will be released (phosphatase reaction). It means that the pyrophosphoric acid was consumed vainly without generating nucleoside-5′-phosphate. On the other hand, if a nucleoside attacks the reaction intermediate, the phosphate group will form a phosphomonoester linkage with the nucleoside, and the generated nucleoside-5′-phosphate will dissociate from EB-AP

(transphosphorylation reaction). It means that the pyrophosphoric acid was utilized for the production of nucleoside-5′-phosphate. That is, if water binds to the reaction intermediate, phosphatase activity will be exerted, and if the nucleoside binds to the intermediate, transphosphorylation activity will be exerted. If the affinity of EB-AP for the nucleoside is increased, i.e., if the Km value is decreased, the likelihood of the transphosphorylation reaction will become high. Further, if the hydrophobicity around the phosphate binding site is increased and thus it becomes difficult for water to approach the binding site, the phosphatase activity will become weaker and the transphosphorylation activity will become relatively stronger. Thus, the expression of "nucleoside-5′-phosphate producing ability is improved" used for the present invention may mean either improvement of the transphosphorylation activity or decrease of the phosphatase activity of a mutant acid phosphatase (see WO96/37603), or it may mean the both.

The details will be described in Example 11.

(7) By using *Escherichia coli* JM109 transformed with the plasmid containing a mutant EB-AP gene, in which the Km value is decreased and the transphosphorylation activity is increased, experimental production of 5′-inosinic acid from inosine is performed. The reaction is performed at 30°C for 45 hours, and the variation

with time in the production amount of 5'-inosinic acid is monitored. The details will be described in Example 13.

If mutation sites that decrease Km are found out, a mutant enzyme having improved affinity for a nucleoside and higher productivity can be produced by combining two or more mutations. By repeating the site-specific mutagenesis, two or more mutation sites can be cumulatively introduced. Further, upon introduction of site-specific mutations, if primers having mixed nucleotides as the nucleotides of a portion coding for an amino acid residue for which the mutation is introduced, a library of mutant genes in which a particular encoded amino acid is replaced with all of amino acid residues can be produced. If a mutation is introduced into multiple sites by using primers having mixed nucleotides, a library of mutant genes coding for extremely many kinds of mutant enzymes can be produced. It is also effective to introduce a library constructed as described above into *Escherichia coli*, and select a mutant comprising a combination of amino acid substitutions providing high activity from the expressed library.

Other than EB-AP, an enzyme having an active site similar to that of EB-AP and a space for binding of a nucleoside may potentially be utilized for the production of nucleoside-5'-phosphate. The active site

must have amino acid residues indispensable for the activity, and the residues must be configured in a suitable relationship in special positions. In EB-AP, Lys115, Arg122, His150, Arg183 and His189 are indispensable for the activity, and it is possible to define the relationship of special positions with distances between Cα's of these 5 residues. In the present invention, since crystal structures of three kinds of EB-AP, wild-type, G74D/I153T mutant and reaction intermediate analogue, were determined, Cα interatomic distances of the active residues in each structure were measured, and summarized in Table 1. Since the distance distribution for each of the distances shown in Table 1 showed a range of about 1Å, it was considered that the desired active site could be formed if each distance is in the range of from a distance shorter than the shortest distance by 1Å (Table 1, lower limit) to a distance longer than the longest distance by 1Å (Table 1, upper limit). In Fig.1, positional relationship of the five residues is shown with upper limits and lower limits of the distances between Cα's.

In Example 8, it will be demonstrated that, in MM-AP, which is an analogous enzyme of EB-AP, all the interatomic distances between active residues fall within the ranges defined based on the three-dimensional structure of EB-AP. In that example, although not a

wild-type, but the G72D/I151T mutant was exemplified, it is considered that there is not significant difference in the active site structure between a wild-type and a mutant of the same enzyme. This assumption is supported by the fact that the structures of the active sites in a wild-type and the G74D/I153T mutant of EB-AP are basically identical to each other (see Table 1).

Table 1

		Wild-type	G74D/I153 T mutant	Reaction intermediat e analogue	Lower limit	Upper limit
Lys115	Arg122	11.6Å	11.6Å	11.4Å	10.4Å	12.6Å
	His150	12.4Å	12.3Å	12.8Å	11.3Å	13.8Å
	Arg183	16.4Å	16.3Å	15.5Å	14.5Å	17.4Å
	His189	12.6Å	12.1Å	11.7Å	10.7Å	13.6Å
Arg122	His150	13.2Å	13.6Å	14.2Å	12.2Å	15.2Å
	Arg183	10.4Å	10.5Å	10.8Å	9.4Å	11.8Å
	His189	5.6Å	5.5Å	5.7Å	4.5Å	6.7Å
His150	Arg183	8.4Å	8.8Å	7.7Å	6.7Å	9.8Å
	His189	9.8Å	10.0Å	10.0Å	8.8Å	11.0Å
Arg183	His189	5.5Å	5.8Å	5.7Å	4.5Å	6.8Å

In order to convert a nucleoside into nucleoside-5′-phosphate by phosphorylation, the presence of the active site that consists of the aforementioned five residues alone is not sufficient, and a nucleoside must be able to bind to a suitable position. In EB-AP, in the neighborhood of phosphate group, a slot-like space suitable for binding of a nucleoside is present on the surface of the molecule [(Fig. 3): it can be displayed on computer graphics (CG) by using the atomic

coordinates represented in the appended Figs. 10-45]. This slot is defined as a space surrounded by four residues of Leu16, Ser72, Glu104 and His189. Even if an enzyme has the active site, the enzyme is unsuitable as a nucleoside-5′-phosphate producing enzyme without a suitable space for binding of a nucleoside.

The mutant nucleoside-5′-phosphate producing enzyme of the present invention can be obtained by modifying an enzyme having the transphosphorylation activity and/or the phosphatase activity, in which the distances between Cα's of five residues of Lys115, Arg122, His150, Arg183 and His189 are within the ranges shown in Fig. 1. However, so long as it has a space for binding of a nucleoside near the aforementioned five residues and has transphosphorylation activity, the distances between Cα's of the five residues may not be within the ranges shown in Fig. 1. Nonetheless, the mutant acid phosphatase to be obtained is preferably has the distances between Cα's of the aforementioned five residues falling within the ranges shown in Fig. 1.

The present invention further provides a mutant EB-AP comprising a replacement of Ser72 with another amino acid, preferably with any one of Phe, Tyr, Trp, Val, Leu, Glu, Asp, Gln, Met, Thr, Arg and Lys, and, in addition, two mutations of G74D and I153T, which are already published as mutations enhancing the nucleoside-5′-phosphate producing ability (henceforth referred to

as the "3-residue replaced mutant EB-AP"). Furthermore, the residues present within a distance of 10Å from Ser72 (residue numbers: 16, 70-71, 73-76, 100, 102-104, 106-108, 115, 148-154, 183) are very likely to interact with a nucleoside, and the present invention also provides a mutant EB-AP comprising one or more replacements of these amino acid residues with one or more other amino acids. The term "replacement (substitution)" used herein include not only an artificial replacement of amino acid residue, but also selection of another acid phosphatase belonging to the same enzyme family as EB-AP and comprising a naturally occurring replacement. However, the present invention is still able to provide a mutant EB-AP containing a mutation point other than the aforementioned amino acid residues.

Further, another acid phosphatase belonging to the same enzyme family as EB-AP may be used for the production of nucleoside-5'-phosphate, if an amino acid mutation homologous to those used for EB-AP is made in that enzyme. As such an acid phosphatase, there can be mentioned those enzymes derived from *Escherichia* bacteria other than *Escherichia blattae*, *Morganella* bacteria other than *Morganella morganii*, *Providencia* bacteria such as *Providencia stuartii*, *Enterobacter* bacteria, *Klebsiella* bacteria such as *Klebsiella planticola* and so forth. However, the amino acid

residues of EB-AP do not necessarily correspond to the amino acid residues of the same numbers in other acid phosphatases. For example, Ser72 of EB-AP corresponds to Ala70 in MM-AP. The correspondence of amino acid residues in two ~~of~~ different proteins can be determined by alignment of the amino acid sequences (Sequence Alignment) when the identity between the both amino acid sequences is about 20% or more, or alignment of the three-dimensional structure and amino acid sequence (Threading) when the identity between the both amino acid sequences is about 20% or less. The former can be performed with a program of BLAST etc., and the latter can be performed with a program of INSIGHT II etc.

The amino acid sequence alignment of EB-AP and a wild-type acid phosphatase (wild-type EA-AP) derived from *Enterobacter aerogenes* obtained by using BLAST is described in Example 20 (see Fig. 9). Further, alignment of the amino acid sequences of EB-AP, MM-AP and acid phosphatases derived from *Salmonella typhimurium* and *Zymomonas mobilis* is shown in Fig. 2. The sequences of the genes coding for EB-AP, MM-AP, acid phosphatases derived from *Salmonella typhimurium* and *Zymomonas mobilis* and EA-AP and amino acid sequences thereof are shown in SEQ ID NOS: 1-10. Among these sequences, EA-AP is of 10-residue replaced mutant, and others are of wild-type. Further, EA-AP is represented as a proprotein containing a signal peptide. In

addition, the amino acid sequences of the acid phosphatase derived from *Providencia stuartii* (GenBank accession X64820) and *Klebsiella planticola* (GenBank accession E16588) and the nucleotide sequences of the genes coding for them are known.

When acid phosphatase is produced as a precursor protein having a signal peptide and then processed into a mature protein through removal of the signal peptide, alignment is performed for the amino acid sequence of the mature protein.

As for BLAST, a file compatible with a computer to be used can be obtained from the files stored in /blast/executable from ncbi.nlm.nih.gov by using FTP.

The details about the operation method are described in http://genome.nhgri.nih.gov/blastall/blast install.

While the improvement of nucleoside-5'-phosphate producing ability is often attained by enhancement of affinity for a nucleoside, besides it, it may also be attained by improvement in reaction rate, shift of optimum pH, enhancement of thermal stability etc. The shift of optimum pH can be attained by changing pK of active residues (Protein Engng., 11, 383-388 (1998)). The enhancement of thermal stability can be attained by introduction of proline residues, replacement of residues that show left-handed helical structure with glycine residues (Protein Engng., 6, 85-91 (1993)),

filling space in the protein (Biochemistry, 32, 6171-6178 (1993)) and so forth.

Further, the mutant nucleoside-5'-phosphate producing enzyme of the present invention may have mutations of other amino acid residues in addition to the aforementioned mutations, so long as such mutations do not adversely affect the nucleoside-5'-phosphate producing ability. Examples of such mutations include~~, for example,~~ a mutation that enhances temperature stability (refer to Japanese Patent Laid-open (Kokai) No. 10-201481/1998). In addition, a single mutation may exert the effect for improvement of the nucleoside-5'-phosphate producing ability and another effect, for example, for improvement of temperature stability. In any case, an enzyme containing such a mutation falls within the scope of the mutant nucleoside-5'-phosphate producing enzyme of the present invention, so long as its nucleoside-5'-phosphate producing ability is eventually enhanced.

For example, the nucleoside-5'-phosphate producing ability may be enhanced even by replacing a residue that is not Ser72 of EB-AP or is not present within a distance of 10Å from the Ser72 with another residue. Examples of such a residue include Leu140 for EB-AP and Leu138 for EA-AP.

As described in detail above, the three-dimensional structure is effective for producing a

mutant of which affinity for a nucleoside and nucleoside-5'-phosphate producing ability are improved. However, the three-dimensional structure is effective not only in changing the affinity for a nucleoside of an enzyme, but also in changing affinity for a phosphate donor. As disclosed in Japanese Patent Laid-open (Kokai) No. 9-37785/1997, the enzyme can use various phosphoric acid ester compounds such as polyphosphoric acid (salt thereof), phenyl phosphate (salt thereof), acetyl phosphate (salt thereof) and carbamyl phosphate (salt thereof) as a phosphate donor. However, it is also possible to broaden its substrate specificity for the phosphate donor, or improve the utilization factor of phosphate by designing a mutation that increases the affinity for a phosphoric acid ester compound in a manner similar to that for designing a mutation enhancing the affinity for a nucleoside.

<u>Brief Explanation of the Drawings</u>

Fig. 1 shows the five amino acid residues serving as the components of the active site having the phosphatase activity or the transphosphorylation activity, and their relationship in special positions as distances between Cα atoms.

Fig. 2 shows alignment of the amino acid sequence of EB-AP with the amino acid sequences of the acid phosphatases derived from *Morganella morganii*,

Salmonella typhimurium and *Zymomonas mobilis*.

Fig. 3 is a photograph of computer graphics (CG), which represents a crystal structure in a binding mode model of the EB-AP reaction intermediate analogue and inosine.

Fig. 4 is a photograph of CG, which shows a crystal structure of the hexamer molecule of EB-AP.

Fig. 5 is a photograph of CG, which shows a crystal structure of a subunit of EB-AP.

Fig. 6 shows a structure of the active site of EB-AP.

Fig. 7 shows primer sets used for site-directed mutagenesis.

Fig. 8 shows primer sets used for site-directed mutagenesis.

Fig. 9 shows the result of amino acid sequence alignment of EB-AP and a wild-type acid phosphatase derived from *Enterobacter aerogenes* (wild-type EA-AP) performed by using the program BLAST.

Fig. 10 shows the crystallographic data (1) for the structure of EB-AP.

Fig. 11 shows the crystallographic data (2) for the structure of EB-AP.

Fig. 12 shows the crystallographic data (3) for the structure of EB-AP.

Fig. 13 shows the crystallographic data (4) for the structure of EB-AP.

Fig. 14 shows the crystallographic data (5) for the structure of EB-AP.

Fig. 15 shows the crystallographic data (6) for the structure of EB-AP.

Fig. 16 shows the crystallographic data (7) for the structure of EB-AP.

Fig. 17 shows the crystallographic data (8) for the structure of EB-AP.

Fig. 18 shows the crystallographic data (9) for the structure of EB-AP.

Fig. 19 shows the crystallographic data (10) for the structure of EB-AP.

Fig. 20 shows the crystallographic data (11) for the structure of EB-AP.

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Fig. 31 shows the crystallographic data (22) for the structure of EB-AP.

Fig. 32 shows the crystallographic data (23) for the structure of EB-AP.

Fig. 33 shows the crystallographic data (24) for the structure of EB-AP.

Fig. 34 shows the crystallographic data (25) for the structure of EB-AP.

Fig. 35 shows the crystallographic data (26) for the structure of EB-AP.

Fig. 36 shows the crystallographic data (27) for the structure of EB-AP.

Fig. 37 shows the crystallographic data (28) for the structure of EB-AP.

Fig. 38 shows the crystallographic data (29) for the structure of EB-AP.

Fig. 39 shows the crystallographic data (30) for the structure of EB-AP.

Fig. 40 shows the crystallographic data (31) for the structure of EB-AP.

Fig. 41 shows the crystallographic data (32) for the structure of EB-AP.

Fig. 42 shows the crystallographic data (33) for the structure of EB-AP.

Fig. 43 shows the crystallographic data (34) for the structure of EB-AP.

Fig. 44 shows the crystallographic data (35) for the structure of EB-AP.

Fig. 45 shows the crystallographic data (36) for the structure of EB-AP.

Best Mode for Carrying out the Invention

Hereafter, the present invention will be explained more specifically with reference to the following examples. However, the present invention is not limited to these examples.

Example 1: Crystallization of wild-type EB-AP

Crystallization was performed by using vapor diffusion in the hanging drop method. A 20 mM sodium phosphate buffer (pH 8.0) containing the wild-type EB-AP (concentration: 10 mg/ml) and a 100 mM Tris-HCl buffer containing 45% (w/v) of polyethylene glycol 400 in the same amounts (7-10 μl each) were dropped and mixed on siliconized cover glass, and a well filled with 500 μl of 100 mM Tris-HCl buffer containing 45% (w/v) of polyethylene glycol 400 was covered with the cover glass

so that a drop of the mixed solution should be hung above the well and left stand at 20°C. Crystals appeared within a few days, and they grew up to hexagonal columnar crystals in a measurable size (about 0.3 x 0.3 x 1.2 mm) within 1 to 2 weeks. For the X-ray data measurement, the crystals were transferred into 100 mM Tris-HCl buffer (pH 8.0) containing 50% (w/v) polyethylene glycol 400.

Upon handling of these crystals, it was necessary to pay attention to the following points. 1) Since the crystals were very likely to collapse by contacting with a container or tools when crystals were taken out from the droplet, the crystallization scheme of the sitting drop method could not be used (although crystals grew), the hanging drop method described herein was used. 2) Since crystals would degrade during measurement and hence resolution would be gradually reduced if the measurement was performed at room temperature, it was necessary to perform the measurement at a low temperature. The time required for mounting the crystals on a stage was made as short as possible to prevent them from being exposed to air.

Using an X-ray diffraction apparatus, R-AXIS IIc of Rigaku Co., Ltd., X-ray diffraction data were collected and crystallographic parameters were determined. The space group was determined to be $P6_322$ and the cell parameters to be a = b = 124.4Å and c =

97.7Å. Assuming that one subunit having a molecular weight of 25000 is contained in an asymmetric unit, the solvent content of the crystals is determined to be 72%.

Example 2: Crystallization of G74D/I153T mutant EB-AP

Crystallization was performed by using vapor diffusion in the hanging drop method. A 20 mM sodium phosphate buffer (pH 8.0) containing the G74D/I153T mutant EB-AP (concentration: 20 mg/ml) and a 20 mM Tris-HCl buffer containing 38% (w/v) of polyethylene glycol 400 in the same amounts (5 μl each) were dropped and mixed on siliconized cover glass, and a well filled with 500 μl of 20 mM Tris-HCl buffer containing 38% (w/v) of polyethylene glycol 400 was covered with the cover glass so that a drop of the mixed solution should be hung above the well and left stand at 20°C. Crystals appeared within a few days, and they grew up to tabular crystals in a measurable size (about 0.7 x 0.4 x 0.2 mm) within 1 week. For the X-ray data measurement, the crystals were transferred into 100 mM Tris-HCl buffer (pH 8.0) containing 50% (w/v) polyethylene glycol 400.

Using an X-ray diffraction apparatus, R-AXIS IIc of Rigaku Co., Ltd., X-ray diffraction data were collected and crystallographic parameters were determined. The space group was determined to be $P2_12_12_1$ and the cell parameters to be a = 138.0Å, b = 168.3Å and c = 58.2Å. Assuming that one subunit having a

molecular weight of 15000 is contained in an asymmetric unit, the solvent content of the crystals is determined to be 64%.

Example 3: Crystallization of complex of wild-type EB-AP and molybdate (reaction intermediate analogue)

Crystallization was performed by a co-crystallization method by using vapor diffusion in the sitting drop method. A 20 mM sodium phosphate buffer (pH 8.0) containing the wild-type EB-AP (concentration: 10 mg/ml) and a 100 mM Tris-HCl buffer containing 40% (w/v) of polyethylene glycol 400 and 1 mM sodium molybdate in the same amounts (15 μl each) were added dropwise to a hollow of a bridge provided on a well filled with 500 μl of 100 mM Tris-HCl buffer containing 40% (w/v) of polyethylene glycol 400, mixed, and left stand at 20°C. Crystals appeared within a few days, and they grew up to rhomboidal crystals in a measurable size (about 0.3 x 0.3 x 0.3 mm) within 1 to 2 weeks. For the X-ray data measurement, the crystals were transferred into 100 mM Tris-HCl buffer (pH 8.0) containing 50% (w/v) polyethylene glycol 400.

Using an X-ray diffraction apparatus, R-AXIS IIc of Rigaku Co., Ltd., X-ray diffraction data were collected and crystallographic parameters were determined. The space group was determined to be $P3_121$ and the cell parameters to be a = b = 86.6Å and c =

205.3Å. Assuming that three subunits having a molecular weight of 25000 is contained in an asymmetric unit, the solvent content of the crystals is determined to be 58%.

Example 4: Crystal structure analysis of wild-type EB-AP

X-ray diffraction data were collected up to the maximum resolution of 1.9Å. Since the crystals were severely damaged by the irradiation of X-ray at room temperature, they were rapidly cooled to -173°C, and the measurement was performed. Heavy atom derivatives were screened by immersing the crystals into a solution of heavy metal salts. The diffraction data of heavy atom derivative crystals were obtained by using Rigaku R-AXISIIc. Based on a difference Fourier map with respect to the native data, it was found that K_2PtCl_4 provided good heavy atom isomorphic crystals. The coordinates of the only ~~one~~ platinum binding site of K_2PtCl_4 were obtained by using the program RSPS. These coordinates were further refined by using the program MLPHARE, from which the phase was calculated. By using this phase, five mercury binding sites of the second heavy atom derivative $KHgI_4$-KI were determined. The heavy atom parameters for both of K_2PtCl_4 and $KHgI_4$-KI were simultaneously refined by using MLPHARE, and then the phase was improved by performing solvent smoothing and histogram matching by using the program DM. As for

K_2PtCl_4, anomalous scattering data were also used. The electron density map calculated by using this good phase was very clear, and thus almost all of amino acid residues were finely fitted.

The first model was constructed on an electron density map prepared with 2.8Å resolution by using the program QUANTA, and structure refinement was performed by using the program X-PLOR. Electron density was not observed for the six residues at the N-terminus, 135 to 136th residues and one residue at the C-terminus, and thus the structure could not determined uniquely. The final model refined with 1.9Å resolution (Fig. 4 to Fig. 6) contained 222 residues out of the 231 residues in total, 236 water molecules and one molecule of sulfate ion. The sulfate ion was derived from ammonium sulfate used in the purification process, and was considered to fit to the phosphate binding site of the active center. The crystallographic reliability factor (R factor) determined by using reflections of 8 to 1.9Å resolution was 21.5%. The average temperature factor was 26$Å^2$ for protein atoms and 45$Å^2$ for water molecules. When a Ramachandran plot was prepared by using the program PROCHECK, it was demonstrated that 93% of residues other than glycine located in the most preferred domain and 7% located at next preferred domain. One subunit was contained in an asymmetric unit and a hexamer was formed by the crystallographic symmetries. The atomic

coordinates were represented in Fig. 10 to Fig. 45.

Fig. 4 is a CG photograph representing a crystal structure of the hexamer molecule of EB-AP. The flows of α carbon atoms were represented with ribbon models. Further, the sulfate ion marking the active center was represented with a ball model.

Fig. 5 is a CG photograph representing a crystal structure of a subunit of EB-AP. The flows of α carbon atoms were represented with ribbon models. Further, the sulfate ion marking the active center was represented with a ball model.

Fig. 6 shows the structure of the active site of EB-AP. The sulfate ion is represented at the center. The doted lines represent hydrogen bonds.

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Fig. 34 shows the crystallographic data (25) for the structure of EB-AP.

Fig. 35 shows the crystallographic data (26) for the structure of EB-AP.

Fig. 36 shows the crystallographic data (27) for the structure of EB-AP.

Fig. 37 shows the crystallographic data (28) for the structure of EB-AP.

Fig. 38 shows the crystallographic data (29) for the structure of EB-AP.

Fig. 39 shows the crystallographic data (30) for the structure of EB-AP.

Fig. 40 shows the crystallographic data (31) for the structure of EB-AP.

Fig. 41 shows the crystallographic data (32) for the structure of EB-AP.

Fig. 42 shows the crystallographic data (33) for the structure of EB-AP.

Fig. 43 shows the crystallographic data (34) for

the structure of EB-AP.

Fig. 44 shows the crystallographic data (35) for the structure of EB-AP.

Fig. 45 shows the crystallographic data (36) for the structure of EB-AP.

Example 5: Modeling of the binding mode of wild-type EB-AP and 5′-inosinic acid

Since the Km value of inosine for EB-AP exceeds 100 mM, the affinity is not high enough to determine the binding mode by X-ray crystallography. In fact, when compounds serving as an inhibitor of EB-AP such as glucose-6-sulfate and adenosine-thiomonophosphate were soaked into the crystals of wild-type EB-AP and X-ray diffraction data were collected to prepare an electron density map, electron density corresponding to these compounds was not observed. Therefore, it was decided to predict the binding style of 5′-inosinic acid and EB-AP by using computer graphics (so-called docking study). As the program, QUANTA was used. Since a sulfate ion was found at the center of the active site in the crystal structure, the phosphate group of 5′-inosinic acid was superimposed on it. Further, since it was known that mutations of G74D and I153T would reduce the Km value of 5′-inosinic acid for EB-AP, it was judged that 5′-inosinic acid would bind to a position not far from G74 and I153, and decided the position of 5′-

inosinic acid. At that time, the position was decided so that the atoms constituting 5′-inosinic acid and the atoms constituting EB-AP should not interfere with each other. In the model constructed as described above, if I153 is changed to Thr, the γ-oxygen atom of the side chain of the threonine introduced by the replacement and 2′-hydroxyl group of the ribose of inosine form a hydrogen bond. Further, when the electrostatic potential of EB-AP was displayed by using the program GRASP, the positively charged inosine base interacted with a negatively charged domain of the surface of the EB-AP molecule, which suggested that a model was reasonable.

<u>Example 6: Crystal structure analysis of G74D/I153T mutant EB-AP</u>

The G74D/I153T mutant EB-AP has an increased ratio of the transphosphorylation activity relative to the phosphatase activity, and in connection with this fact, the nucleoside-5′-phosphate producing ability is also improved. It is considered that this is caused by the decrease of the Km value for a nucleoside, i.e., improvement of the affinity for a nucleoside. It was expected that the molecular mechanism for improvement of the affinity for a nucleoside should be elucidated by determining the crystal structure of the mutant EB-AP and comparing it with the crystal structure of wild-type

EB-AP.

At room temperature, the X-ray diffraction data were collected to the maximum resolution of 2.4Å. Estimating from the volume of the unit cell, space group and molecular weight of the enzyme, it was expected that one hexamer molecule is contained in the asymmetric unit. Then, as a model for searching the hexamer structure of wild-type EB-AP, analysis was performed by the molecule replacement method using the program amore. Data of 10-3Å resolution were used for the rotation search, and data of 10-4Å resolution were used for the translation search. In the both searches, the correct answer appeared as a top peak. When refinement was performed by considering the molecule as a rigid body, the R factor decreased to 37.3%. Then, structure modification on graphics using QUANTA and structure refinement using X-PLOR were repeated to obtain a model with an R factor of 19.9% at 10-2.4Å resolution.

When a docking model of 5'-inosinic acid and the G74D/I153T mutant EB-AP was prepared in the same manner as in Example 5, it was expected that the γ-oxygen atom of the side chain of ~~the~~ Thr153 introduced by the replacement would form a hydrogen bond with a hydroxyl group of ribose of inosine. By comparing temperature factors, it was found that the fluctuation of the loop containing Asp74 where another replacement was made was larger in the G74D/I153T mutant EB-AP compared with the

wild-type. This loop is expected to interact with the base of inosine, and it is suggested that it becomes more likely to bind to the base due to the larger fluctuation.

Example 7: Crystal structure analysis of the complex of wild-type EB-AP with molybdate (reaction intermediate analogue)

In the enzymatic reaction of EB-AP, a phosphoric acid monoester linkage is first cleaved, and the phosphate group forms a covalent bond with an active site residue, His189. The enzyme molecule in this state is called a reaction intermediate. The reaction intermediate is quickly attacked by water or alcohol, and as a result, a phosphate ion dissociates from it. When water attacks, phosphatase activity will be exerted, and when alcohol attacks, the transphosphorylation activity will be exerted. In the both cases, the reaction intermediate is unstable and it is impossible to determine its structure by X-ray crystallography. However, a complex (reaction intermediate analogue) in which molybdate covalently bonds to His189 instead of phosphate is not attacked by water, and thus it exists stably.

In the transphosphorylation reaction, a phosphate acceptor binds to the reaction intermediate to form a phosphoric acid monoester linkage. Therefore, for the

purpose of modeling the binding mode with a nucleoside, it is more suitable to use a reaction intermediate structure rather than the structure in free form. In order to perform docking study of the reaction intermediate and a nucleoside, the crystal structure of the reaction intermediate analogue was determined.

At room temperature, the X-ray diffraction data were collected to the maximum resolution of 2.4Å. Estimating from the volume of unit cell, space group and molecular weight of the enzyme, it was expected that a half of the hexamer, i.e., three subunits, were contained in the asymmetric unit. Therefore, trimer structure in which the subunits were correlated with one another with a three-fold axis was prepared as a model for searching in the molecule replacement method. Data of 10-3Å resolution were used for the rotation search, and data of 10-4Å resolution were used for the translation search. In the both searches, the correct answer appeared as a top peak. When refinement was performed by considering the molecule as a rigid body, the R factor decreased to 42.4%. Then, structure modification on graphics using QUANTA and structure refinement using X-PLOR were repeated to obtain a model showing an R factor of 22.3% at 8-2.4Å resolution. The asymmetric unit contained a half of the hexamer, i.e., three subunits.

Example 8: Crystallization and crystal structure analysis of G72D/I151T mutant enzyme derived from acid phosphatase of *Morganella morganii* (MM-AP)

Crystallization of G72D/I151T double mutation mutant of MM-AP was performed by using vapor diffusion in the hanging drop method. A solution of the protein (concentration: 40 mg/ml) and a 125 mM citrate buffer (pH 4.8) containing 25% (w/v) of polyethylene glycol 1000, 25 mM ammonium sulfate and 25 mM DTT in the same amounts (5 μl each) were dropped and mixed on siliconized cover glass, and a well filled with 500 μl of 125 mM citrate buffer (pH 4.8) containing 25% (w/v) of polyethylene glycol 1000, 25 mM ammonium sulfate and 25 mM DTT was covered with the cover glass so that a drop of the mixed solution should be hung above the well and left stand at 20°C. Crystals appeared within a few days, and they grew up to a measurable size (about 0.4 x 0.4 x 0.3 mm) within 1 week.

Using an X-ray diffraction apparatus, R-AXIS IIc of Rigaku Co., Ltd., X-ray diffraction data were collected to determine crystallographic parameters. The space group was determined to be $P2_12_12_1$ and the cell parameters to be a = 90.64 Å, b = 119.74 Å and c = 136.14 Å. The diffraction data to 2.6 Å resolution data were measured at 100 K on the synchrotron radiation light facility BL-6B at the HIGH ENERGY ACCELERATOR RESEARCH ORGANIZATION, Tsukuba.

Estimating from the volume of unit cell, space group and molecular weight of the enzyme, it was expected that one hexamer molecule was contained in the asymmetric unit. Then, by using the hexamer structure of wild-type EB-AP as a model for searching, the molecule replacement method was performed using the program amore. Data of 10-3Å resolution were used for the rotation search, and data of 10-4Å resolution were used for the translation search. In the both searches, the correct answer appeared as a top peak. After refinement was performed by considering the molecule as a rigid body, structure modification on graphics using QUANTA and structure refinement using X-PLOR were repeated to obtain a model with an R factor of 0.197% at 10-2.6Å resolution.

The distances between Cα atoms of the five active residues shown in Fig. 1 (Lys113, Arg120, His148, Arg181 and His187) are shown in Table 2. It was confirmed that, in MM-AP that is an analogous enzyme of EB-MP, all of the interatomic distances between the active residues fell within the ranges defined based on the three-dimensional structure of EB-AP.

Table 2

		G72D/I151T mutant MM-AP	Lower limit	Upper limit
Lys113	Arg120	11.3Å	10.4Å	12.6Å
	His148	12.6Å	11.3Å	13.8Å
	Arg181	16.3Å	14.5Å	17.4Å
	His187	12.5Å	10.7Å	13.6Å
Arg120	His148	14.0Å	12.2Å	15.2Å
	Arg181	10.9Å	9.4Å	11.8Å
	His187	6.1Å	4.5Å	6.7Å
His148	Arg181	8.9Å	6.7Å	9.8Å
	His187	10.2Å	8.8Å	11.0Å
Arg181	His187	5.4Å	4.5Å	6.8Å

Example 9: Modeling of the binding mode of EB-AP reaction intermediate and inosine

A binding mode model was constructed on computer graphics by using QUANTA (Fig. 3). Molybdate was replaced with phosphate as it was. Inosine was placed near the nucleoside portion of 5′-inosinic acid in the binding mode model of wild-type EB-AP and 5′-inosinic acid. However, the degree of freedom was of course higher than the docking with 5′-inosinic acid, since an inosine did not have a phosphoric acid monoester linkage. Therefore, fine adjustment of the position of inosine was performed so that inosine should bind to the molecular surface of EB-AP in a more preferred condition to obtain a binding style model. For the subsequent designing of a mutant enzyme, this model was used.

Example 10: Design of mutant EB-AP aiming at enhancement

<u>of affinity for nucleoside</u>

According to the model constructed in Example 8, it was suggested that the side chain of Ser72 might interact with the base of inosine. It was expected that, if this residue was replaced with an aromatic amino acid such as phenylalanine, tyrosine and tryptophan, the π-π interaction would be generated between an aromatic ring and a nucleoside base and thus the affinity of nucleoside for EB-AP would be improved. Similarly, it was expected that, if it was replaced with an amino acid having a branched hydrophobic group in the side chain such as valine, leucine and isoleucine, the CH/π interaction would be generated between the branched hydrophobic group in the side chain and the nucleoside base, or if it was replaced with a negatively charged amino acid such as glutamic acid and an aspartic acid, it would be electrostatically attracted by the positive charge of the nucleoside base, and thus the affinity would be improved. Therefore, in order to further enhance the transphosphorylation activity of the G74D/I153T mutant EB-AP of which transphosphorylation activity was relatively increased compared with the phosphatase activity, S72F, S72Y, S72W, S72V, S72E and S72D mutants of this mutant EB-AP were prepared. In addition, mutants in which S72 was replaced with the other amino acids were also produced. Incidentally, these mutants would become a 3-residue replaced mutant

EB-AP.

<u>Example 11: Construction of 3-residue replaced mutant of EB-AP in which Ser72 is replaced with another amino acid</u>

In order to construct a mutant EB-AP for expression in *Escherichia coli* JM109, a plasmid pEPI340 containing a gene for G74D/I153T mutant EB-AP was used as a template for site-directed mutagenesis utilizing PCR. The nucleotide sequences of these plasmids pEPI305 and pEPI340 are disclosed in Japanese Patent Laid-open (Kokai) No. 10-201481/1998, paragraph (0143), Table 12. A strain of *Escherichia coli* JM109 harboring the plasmid pEPI305 was designated as AJ13144, and deposited as an international deposition at the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry (postal code 305-8566, 1-3, Higashi, 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) on February 23, 1996, and it received an accession number of FERM BP-5423 [refer to the description of the aforementioned patent document, paragraphs (0105) to (0110)].

The mutation was introduced by using Quick Change site-directed mutagenesis kit available from Stratagene, United States, and primers corresponding to each mutant enzyme (Fig. 7, SEQ ID NOS: 11-61) according to the manufacturer's protocol. *Escherichia coli* XL-1 was transformed with the PCR product. The transformed cells

were plated on an L agar medium plate containing 100 μl/ml of ampicillin, and incubated at 37°C for 16 hours. The produced colonies were collected, and cultured overnight in L medium containing 100 μl/ml of ampicillin with shaking. The cells were collected from the medium by centrifugation, and the plasmid was extracted by using FlexiPrep Kit available from Pharmacia (Sweden) according to the manufacturer's protocol. The nucleotide sequences coding for the various 3-residue replaced mutant EB-AP were confirmed by DNA sequence analysis.

The synthesis of the primers shown in Fig. 7 was consigned to Japan BioService Co., Ltd.

Example 12: Measurement of transphosphorylation activity and reaction rate constants of mutant EB-AP

Escherichia coli JM109 transformed with a plasmid containing a gene for one of various 3-residue replaced mutant EB-AP's was inoculated into 50 ml of L medium containing 100 μl/ml of ampicillin and cultured at 37°C for 16 hours. The cells were collected by centrifugation from the medium, suspended in 3 ml of 25 mM phosphate buffer (pH 7.0), and disrupted by sonication at 4°C for 20 minutes. The insoluble fraction in the sonicated suspension was removed by centrifugation to prepare a cell free extract. The expression of each EB-AP 3-residue replaced mutant

enzyme was confirmed by SDS-PAGE. The expression amount was about 20% of the total protein.

The transphosphorylation activity of the cell free extract was measured under the following conditions. A reaction mixture (1 ml) containing 2 mM inosine, 100 mM sodium pyrophosphate, 100 mM acetate buffer (pH 4.0) and 100 μl of the cell free extract was incubated at pH 4 and 30°C for 10 minutes. After 200 μl of 1 N hydrochloric acid was added to stop the reaction, the precipitates were removed by centrifugation, and the produced 5′-inosinic acid was quantified. The transphosphorylation activity of each 3-residue replaced mutant EB-AP was represented with a relative activity, which was a ratio of the amount of 5′-inosinic acid produced by the 3-residue replaced mutant over that produce by the G74D/I153T mutant, to which the third mutation was introduced.

Then, the Km value for inosine in the transphosphorylation reaction by each 3-residue replaced mutant EB-AP was measured under the following conditions. A reaction mixture (1 ml) containing 100 mM sodium pyrophosphate, 100 mM acetate buffer (pH 4.0), 10-100 mM inosine and 100 μl of the cell free extract was incubated at pH 4 and 30°C for 10 minutes. After 200 μl of 1 N hydrochloric acid was added to stop the reaction, the precipitates were removed by centrifugation, and the produced 5′-inosinic acid was quantified. The Km value

was calculated by the Hanes-Woolf plotting. The results are shown in Table 3.

Table 3

	Km value	Transphosphorylation activity
S72F/G74D/I153T	20 mM	2.80
S72Y/G74D/I153T	25 mM	2.04
S72W/G74D/I153T	30 mM	1.71
S72D/G74D/I153T	33 mM	1.59
S72V/G74D/I153T	40 mM	2.46
S72E/G74D/I153T	40 mM	3.19
S72M/G74D/I153T	46 mM	1.94
S72T/G74D/I153T	50 mM	1.91
S72L/G74D/I153T	57 mM	2.24
S72R/G74D/I153T	59 mM	1.99
S72Q/G74D/I153T	77 mM	2.42
S72K/G74D/I153T	78 mM	1.53
S72P/G74D/I153T	109 mM	1.34
S72A/G74D/I153T	115 mM	0.78
S72N/G74D/I153T	124 mM	0.43
S72G/G74D/I153T	137 mM	0.43
S72H/G74D/I153T	N.D.	N.D.
G74D/I153T	100 mM	1.00
10-Residue replaced mutant enzyme	40 mM	1.44

In Example 10, all of the mutants expected to have improved affinity for inosine due to the π-π interaction, the CH/π interaction and the electrostatic interaction (S72F, S72Y, S72W, S72V, S72E, S72D) showed decreased Km value for inosine compared with that of the G74D/I153T mutant EB-AP, in which Ser72 is unchanged, and thus they showed improved affinity for inosine. Further, they also showed improvement in transphosphorylation activity. In particular, the S72F mutant showed marked

improvements in both of the Km value and the transphosphorylation activity. It is estimated that the aromatic ring of phenylalanine and the inosine base caused the π-π interaction in suitable positional relationship, and thus the affinity was improved. The Km values of S72M, S72T, S72R, S72Q and S72K mutants also decreased. It was considered that some preferred interactions such as hydrophobic interaction and formation of hydrogen bonds were caused between these amino acid residues and the nucleoside base. Incidentally, a gene could not be produced for S72I. Further, considering the possibility that the S72C mutation causes an erroneous S-S bond, it was not produced.

5′-Inosinic acid was analyzed by high performance liquid chromatography (HPLC) under the following conditions.

Column: Cosmosil 5C18-AR (4.6 x 150 mm), produced by Nakarai Tesque

Mobile phase: 5 mM potassium phosphate buffer (pH 2.8)/ methanol = 95/5

Flow rate: 1.0 ml/min

Temperature: room temperature

Detection: UV 245 nm

Example 13: Production of 5′-inosinic acid using *Escherichia coli* JM109 to which S72F/G74D/I153T mutant

EB-AP gene is introduced

Escherichia coli JM109 transformed with a plasmid containing a gene for G74D/I153T mutant, 10-residue replaced mutant or S72F/G74D/I153T mutant EB-AP was inoculated into 50 ml of L medium containing 100 μg/ml of ampicillin and 1 mM of IPTG, and cultured at 37°C for 16 hours.

Cells of *Escherichia coli* JM109 introduced with each of the aforementioned mutant EB-AP genes were added at a density of 100 mg/dl in terms of dry cell weight to a solution in an acetate buffer (pH 4.0) containing 12 g/dl of pyrophosphoric acid and 6 g/dl of inosine, and reaction was performed at 30°C for 24 hours while pH was maintained at 4.0. The results of measurement of the produced amount of 5′-inosinic acid are shown in Table 4. The produced inosinic acid consisted only of 5′-inosinic acid, and 2′-inosinic acid and 3′-inosinic acid byproducts were not observed at all.

In the reaction utilizing *Escherichia coli* JM109 introduced with the plasmid containing the G74D/I153T mutant EB-AP gene, 7.5 g/dl of 5′-inosinic acid was produced and accumulated, but the accumulation did not increase even if the reaction time was prolonged. In the reaction utilizing *Escherichia coli* JM109 introduced with the plasmid containing the 10-residue replaced mutant EB-AP gene, the accumulation was improved, and 12.1 g/dl of 5′-inosinic acid was produced and

accumulated. In the reaction utilizing *Escherichia coli* JM109 transformed with the plasmid containing the S72F/G74D/I153T mutant EB-AP gene, which was designed and constructed based on the three-dimensional structure, the productivity was further improved, and 13.2 g/dl of 5′-inosinic acid was produced and accumulated.

Table 4

Introduced mutant enzyme gene	Produced inosinic acid (g/dl)
G74D/I153T	7.5
10-Residue replaced mutant	12.1
S72F/G74D/I153T	13.2

Example 14: Measurement of transphosphorylation activity and reaction rate constant of 3-residue replaced mutant EB-AP, in which L16W, S71W, S73W, E104F or E104W mutation is introduced

Since it was considered that the S72F mutation improved the affinity for inosine by the π-π interaction, other amino acid residues that could be expected to cause the π-π interaction with the inosine base by replacement with an aromatic amino acid were searched on computer graphics. As a result, there was suggested possibility that an aromatic ring introduced by ~~replacement by mutations of~~ L16W, S71W, S73W, E104F and E104W might interact with the inosine base. Therefore, these five kinds of 3-residue replaced mutant EB-AP's were prepared (based on the G74D/I153T mutant EB-AP) by

the method described in Example 11 (primers corresponding to each mutant enzyme were shown in Fig. 8A, SEQ ID NOS: 62-76), and their transphosphorylation activity and reaction rate constant were measured by the method described in Example 12. The results are shown in Table 5. Although the transphosphorylation activity decreased in all of the mutant enzymes, the Km value decreased in all of the mutant enzymes and thus it was suggested that the affinity for inosine was improved. Although Leu16 was separated by 10Å (in terms of the distance between Cα's) from Ser72, which was considered to surely interacts with inosine, it was demonstrated that the interaction with inosine was possible, even if it was separated by such a distance.

The synthesis of the primer sets shown in Fig. 8A was consigned to Japan BioService Co., Ltd.

Table 5

	Km value	Transphosphorylation activity
L16W/G74D/I153T	33 mM	0.21
S71W/G74D/I153T	75 mM	0.26
S73W/G74D/I153T	29 mM	0.77
E104F/G74D/I153T	61 mM	0.65
E104W/G74D/I153T	67 mM	0.26
G74D/I153T	100 mM	1.00
10-Residue replaced mutant enzyme	40 mM	1.44

Example 15: Construction of 10-residue replaced mutant EB-AP, in which A72F or A72E mutation is introduced, and

<u>measurement of transphosphorylation activity and reaction rate constant thereof</u>

The S72F mutation that decreased the Km value in the highest degree and the S72E mutation that enhanced the activity in the highest degree in Example 12 were introduced into the 10-residue replaced mutant EB-AP. Since Ser72 was replaced with Ala in the 10-residue replaced mutant EB-AP, the A72F and A72E mutations were actually introduced. When a wild-type EB-AP is considered as standard, ten residues were replaced in the both. These two kinds of mutants were produced by the method described in Example 11 (primers corresponding to each mutant enzyme are shown in Fig. 8B, SEQ ID NOS: 77-82). As a template for site-directed mutagenesis utilizing PCR, plasmid pEMP370 (Japanese Patent Laid-open (Kokai) No. 9-37785/1997, Example 19) containing a 10-residue replaced mutant EB-AP gene was used. Furthermore, transphosphorylation activity and reaction rate constant were measured by the method described in Example 12. The results are shown in Table 6. The transphosphorylation activity was represented in terms of relative activity, which was a ratio of the amount of 5′-inosinic acid produced by the 3-residue replaced mutant over that produce by the G74D/I153T mutant, to which the third mutation was introduced.. In both of the mutant enzymes, the Km value markedly decreased. As for the transphosphorylation activity, it

was decreased by the A72F mutation, whereas it was increased by A72E mutation.

Table 6

	Km value	Transphosphorylation activity
A72F/10-residue replaced mutant enzyme	9 mM	0.11
A72E/10-residue replaced mutant enzyme	15 mM	2.30
10-residue replaced mutant enzyme	40 mM	1.44

<u>Example 16: Production of 5′-inosinic acid utilizing *Escherichia coli* JM109 to which gene for A72F/10-residue replaced mutant EB-AP or gene for A72E/10-residue replaced mutant EB-AP is introduced</u>

Experimental production of 5′-inosinic acid was performed by the method described in Example 13 using *Escherichia coli* JM109 transformed with a plasmid containing the genes for A72E/10-residue replaced mutant or A72F/10-residue replaced mutant EB-AP. The results are shown in Table 7. The accumulation amount of 5′-inosinic acid increased in the both mutants.

Table 7

Introduced mutant enzyme gene	Produced inosinic acid (g/dl)
A72F/10-residue replaced mutant	13.9
A72E/10-residue replaced mutant	13.9
10-residue replaced mutant	12.1

Example 17: Construction of mutant EB-AP, in which I103D and T153N mutations are introduced, and measurement of transphosphorylation activity and reaction rate constant

The model shown in Fig. 3 suggested that Asp introduced by the I103D mutation caused electrostatic interaction with the inosine base and Asn introduced by the T153N mutation formed a hydrogen bond with a hydroxyl group of ribose. Therefore, I103D/G74D/I153T mutant EB-AP and G74D/I153N mutant EB-AP were produced by introducing these residues into the G74D/I153T mutant EB-AP in a manner described in Example 11 (primers corresponding to each mutant enzyme were shown in Fig. 8C, SEQ ID NOS: 83-88). Further, transphosphorylation activity and reaction rate constant were measured by the method described in Example 12. The results are shown in Table 8. The transphosphorylation activity was represented in terms of relative activity, which was a ratio of the amount of 5'-inosinic acid produced by the 3-residue replaced mutant over that produce by the G74D/I153T mutant, to which the third mutation was introduced.. In the both mutants, the transphosphorylation activity decreased, whereas the Km value decreased. Thus, it was demonstrated that the affinity for inosine was improved.

Table 8

	Km value	Transphosphorylation activity
I103D/G74D/I153T	51 mM	0.09
G74D/I153N	38 mM	0.18
G74D/I153T	100 mM	1.00

Example 18: Construction of mutant EB-AP in which Leu140 is replaced with Phe, Glu or Lys and measurement of transphosphorylation activity and reaction rate constant

Although Leu140 is separated from Ser72 more than 10Å, it is located at a position immediately adjacent to the phosphate binding site in the three-dimensional structure of the reaction intermediate analogue. Therefore, it was considered that, if this residue was replaced, the structure around the phosphate binding site of the reaction intermediate would be changed, and as a result, the structure and fluctuation of the nucleoside binding site would also be affected. It is expected that, if this residue is replaced with more bulky Phe, positively charged Lys or negatively charged Glu, the affinity for a nucleoside may be changed. It was decided that the mutations should be introduced into the A72E/10-residue replaced enzyme, which showed high transphosphorylation activity in Example 15. These three kinds of mutants were produced by the method described in Example 11 (primers corresponding to each mutant enzyme are shown in Fig. 8D, SEQ ID NOS: 89-97). As a template for site-directed mutagenesis utilizing

PCR, a plasmid containing the gene for A72E/10-residue replaced mutant EB-AP was used. Furthermore, transphosphorylation activity and reaction rate constant were measured by the method described in Example 12. The results are shown in Table 9. The transphosphorylation activity was represented in terms of relative activity, which was a ratio of the amount of 5'-inosinic acid produced by the 3-residue replaced mutant over that produce by the G74D/I153T mutant, to which the third mutation was introduced.

Table 9

	Km value	Transphosphorylation activity
A72E/L140F/10-residue replaced mutant enzyme	9 mM	1.66
A72E/L140K/10-residue replaced mutant enzyme	78 mM	0.07
A72E/L140E/10-residue replaced mutant enzyme	322 mM	0.16
A72E/10-residue replaced mutant enzyme	15 mM	2.30

The mutant, in which L140F mutation is introduced, showed decreased Km value. Conversely, L140K and L140E mutations markedly increased Km.

Example 19: Purification of wild-type acid phosphatase derived from *Enterobacter aerogenes* IFO12010 and determination of N-terminus amino acid sequence thereof

An acid phosphatase derived from *Enterobacter*

aerogenes IFO12010 was purified from cultured cells of *Escherichia coli* JM109/pENP110 described in Japanese Patent Laid-open (Kokai) No. 10-201481/1998, Example 24, and its N-terminus amino acid sequence was determined to determine the amino acid sequence of the mature protein. *Escherichia coli* JM109/pENP110 is a bacterium prepared by introducing an acid phosphatase gene derived from *Enterobacter aerogenes* IFO12010 into *Escherichia coli* JM109 strain, and it produces the acid phosphatase. The amino acid sequence of a precursor protein deduced from the nucleotide sequence of this acid phosphatase gene corresponds to the sequence shown in SEQ ID NO: 10. The amino acid sequence shown in SEQ ID NO: 10 is an amino acid sequence of L61Q/A63Q/E64A/N67D/S69A/G72D/T133K/E134D/I151T mutant EA-AP.

50 ml of the nutrient medium (pH 7.0) containing 1 g/dl of peptone, 0.5 g/dl of yeast extract and 1 g/dl of sodium chloride was put into 500-ml Sakaguchi flask, and sterilized by heating at 120°C for 20 minutes. One platinum loop of *Escherichia coli* JM109/pENP110 was inoculated into the medium, and cultured at 30°C for 16 hours with shaking. The cells were collected from the medium by centrifugation, suspended in 100 mL of 100 mM potassium phosphate buffer (pH 7.0), and disrupted by sonication at 4°C for 20 minutes. The insoluble fraction in the sonicated suspension was removed by

centrifugation to prepare a cell free extract. Ammonium sulfate was added to this cell free extract to 30% saturation. After the produced precipitates were removed by centrifugation, ammonium sulfate was further added to the supernatant solution to 60% saturation. The produced precipitates were collected by centrifugation and dissolved in 100 mM potassium phosphate buffer. This crude enzyme solution was dialyzed three times against 500 mL of 100 mM potassium phosphate buffer (pH 7.0), then loaded on a DEAE-Toyopearl 650M column (ϕ3.0 x 10.0 cm) equilibrated with 20 mM potassium phosphate buffer (pH 7.0), and washed with 20 mM potassium phosphate buffer (pH 7.0). Since the transphosphorylation activity was found in a passing fraction, that fraction was collected. The fraction was added with ammonium sulfate to 35% saturation, and adsorbed on a Butyl Toyopearl column (ϕ3.0 x 7.0 cm) equilibrated with 20 mM potassium phosphate buffer (pH 7.0) containing 35% saturated ammonium sulfate. The fraction was eluted with a linear concentration gradient of 35% saturated to 20% saturated potassium phosphate buffer (pH 7.0). The active fractions were collected, dialyzed against 1 L of 10 mM potassium phosphate buffer (pH 6.0), and adsorbed on a CM-Toyopearl column (ϕ3.0 x 7.0 cm) equilibrated with 10 mM potassium phosphate buffer (pH 6.0). The fractions were eluted with a linear concentration gradient of potassium phosphate

buffer (pH 6.0) containing 0 mM to 300 mM potassium chloride. The active fractions were collected.

As a result of the above procedure, an enzyme exhibiting transphosphorylation activity was finally purified by about five times from the cell free extract at a recovery ratio of about 16%. This enzyme preparation was confirmed to be uniform by SDS-polyacrylamide gel electrophoresis.

This purified enzyme was adsorbed on a DITC membrane (produced by Milligen/Biosearch), and the amino acid sequence of its N-terminus was determined by using Prosequencer 6625 (produced by Milligen/Biosearch). As a result, the amino acid sequence of the five residues at the N-terminus was determined, which is shown in SEQ ID NO: 98. Since the N-terminus of the purified enzyme was started from the 21st leucine residue (amino acid number 1) of the sequence of SEQ ID NO: 10, it was considered that the amino acid sequence shown in SEQ ID NO: 10 was a sequence of a precursor protein, and the peptide from the 1st methionine residue (amino acid number 20) to the 20th alanine residue (amino acid number 1) was removed after translation. Based on this result, it was considered that the amino acid sequence of the mature protein corresponded to the sequence of the amino acid numbers 1-228 of the sequence shown in SEQ ID NO: 10.

Example 20: Construction of gene for mutant enzyme of acid phosphatase derived from *Enterobacter aerogenes* (EA-AP) and production of 5'-inosinic acid using *Escherichia coli* JM109 to which that gene is introduced

It was decided that a mutation homologous to the three mutations of S72F/G74D/I153T, which enhanced the transphosphorylation activity for inosine in EB-AP, was introduced into EA-AP. The result of alignment of the amino acid sequences of EB-AP and EA-AP (wild-type) performed by using the program BLAST is shown in Fig. 9. It was demonstrated that Ser72/Gly74/Ile153 of EB-AP corresponded to Ala70/Gly72/Ile151 in EA-AP. Therefore, A70F/G72D/I151T mutant EA-AP was produced by the method described in Example 11. 5'-Inosinic acid was produced from inosine by using *Escherichia coli* JM109 transformed with a plasmid containing the mutant enzyme gene by the method described in Example 13. The results are shown in Table 10. The A70F/G72D/I151T mutant EA-AP showed 5'-inosinic acid producing ability comparable to that of the S72F/G74D/I153T mutant EB-AP.

Table 10

Introduced mutant enzyme gene	Produced inosinic acid (g/dl)
EA-AP A72F/G74D/I153T	13.1
EB-AP S72F/G74D/I153T	13.2

Fig. 9 shows the result of amino acid sequence

alignment of EB-AP and the acid phosphatase derived from *Enterobacter aerogenes* (EA-AP) performed by using the program BLAST. The upper row indicates EB-AP and the lower row indicates EA-AP. In the middle row, if the residues of the both are identical, the name of the residue is indicated, and if they are analogous even though they are not identical, + is indicated. The position of the 72nd residue (Ser72) of EB-AP was indicated with [72]. The corresponding residue in EA-AP is Ala70.

<u>Example 21: High expression of enzyme caused by modification of promoter sequence in novel mutant acid phosphatase gene derived from *Enterobacter aerogenes* IFO12010</u>

A site-specific mutation was introduced by a genetic engineering technique into the promoter sequence segment of the gene coding for the mutant acid phosphatase derived from *Enterobacter aerogenes* IFO12010 to construct a gene coding for a mutant acid phosphatase exhibiting increased enzyme expression amount. As a gene for introducing a mutation, a plasmid pENP170 that contained a mutant EA-AP gene coding for L61Q/A63Q/E64A/N67D/S69A/G72D/T133K/E134D/I151T mutant EA-AP was used. pENP170 was prepared as follows.

From a plasmid pENP110 containing the gene coding for a wild-type acid phosphatase derived from

Enterobacter aerogenes IFO12010 obtained by the method described in Japanese Patent Laid-open (Kokai) No. 10-201481/1998, Example 24, a DNA fragment having a size of 1.6 kbp and containing a gene coding for the wild-type acid phosphatase was excised with restriction enzymes SalI and KpnI, and ligated to pUC19 (product produced by Takara Shuzo Co. Ltd.) digested with SalI and KpnI. This plasmid was designated as pENP120. The following mutations were introduced into pENP120 by site-specific mutagenesis to obtain pENP170. The nucleotide sequence of the SalI-KpnI 1.6 kbp DNA fragment in pENP170 was a sequence shown in SEQ ID NO: 9.

72Gly (GGC) -> Asp (G*AC)
151Ile (ATC) -> Thr (A*CC)
61Leu (CTG) -> Gln (C*AG)
63Ala (GCT) -> Gln (*C*A*G)
64Glu (GAA) -> Ala (G*CA)
67Asn (AAC) -> Asp (*GAC)
69Ser (AGC) -> Ala (*G*CC)
133Thr (ACC) -> Lys (A*A*A)
134Glu (GAG) -> Asp (GA*C)

The mutations were introduced into the promoter sequence segment of the mutant EA-AP gene contained in pENP170 by using Quick Change site-directed mutagenesis kit produced by Stratagene. The mutation was introduced

according to the protocol of Stratagene by using oligonucleotides for introduction of mutation, MUT170 (SEQ ID NO: 99) and MUT171 (SEQ ID NO: 100), which were synthesized by using a DNA synthesizer (Model 394 produced by Applied Biosystem), and pENP170 as a template.

Escherichia coli JM109 (produced by Takara Shuzo) was transformed with the obtained plasmid DNA in a conventional manner. The cells were plated on L agar medium containing 100 μg/ml of ampicillin to obtain transformants. A plasmid was prepared from the transformants by the alkali lysis method, and their nucleotide sequence was determined to confirm that the target nucleotides were replaced. The determination of the nucleotide sequences was performed according to the method of Sanger et al. (J. Mol. Biol., 143, 161 (1980)) using Taq DyeDeoxy Terminator Cycle Sequencing Kit (produced by Applied Biochemical).

As described above, a mutant gene was constructed, in which the nucleotide sequence of -10 region of the deduced promoter sequence located upstream from the coding region of the deduced acid phosphatase derived from *Enterobacter aerogenes* IFO12010 was changed from AAAAAT to TATAAT, which was the same as *lac* promoter of *Escherichia coli*. The plasmid containing this mutant gene was designated as pENP180.

Escherichia coli JM109/pENP170 and *Escherichia*

coli JM109/pENP180 introduced with the gene of which -10 region of the promoter sequence was modified were each inoculated to 50 ml of L medium containing 100 μg/ml of ampicillin and 50 ml of L medium containing 100 μg/ml of ampicillin added with 1 mM of IPTG, respectively, and cultured at 37°C for 16 hours. The cells were collected by centrifugation from each medium of each strain, and washed once with physiological saline. The cells of each culture was added in an amount of 100 mg/dl in terms of dry cell weight to a solution containing 15 g/dl of pyrophosphoric acid and 8 g/dl of inosine dissolved in 100 mM acetate buffer (pH 4.0), and allowed to react at 30°C for 1 hour while pH was maintained at 4.0. The amounts of the produced 5'-inosinic acid are shown in Table 11.

Inosine and 5'-inosinic acid were analyzed by high performance liquid chromatography (HPLC) under the following conditions.

Column: Cosmosil 5C18-AR (4.6 x 150 mm, produced by Nakarai Tesque)
Mobile phase: 5 mM potassium phosphate buffer (pH 2.8)/methanol = 95/5
Flow rate: 1.0 ml/min
Temperature: room temperature
Detection: UV 245 nm

Escherichia coli JM109/pENP170 showed low activity with no addition of IPTG, whereas *Escherichia coli* JM109/pENP180 showed high activity even with no addition of IPTG. Further, *Escherichia coli* JM109/pENP180 showed further higher activity with addition of IPTG. Thus, the effectiveness of the modification of the promoter region was demonstrated.

Table 11

Strain	IPTG	Produced 5′-inosinic acid (g/dl)
Escherichia coli JM109/pENP170	Not added	0.73
	Addition of 1 mM	3.09
Escherichia coli JM109/PENP180	Not added	2.86
	Addition of 1 mM	3.37

<u>Example 22: Construction of gene coding for novel mutant acid phosphatase derived from *Enterobacter aerogenes* IFO12010 showing improved affinity for nucleoside</u>

A site specific mutation was introduced into the mutant acid phosphatase gene derived form *Enterobacter aerogenes* IFO12010 constructed in Example 21 by a genetic engineering technique to prepare a gene coding for a mutant acid phosphatase of which affinity for a nucleoside, in particular, guanosine, was improved. As the replacements of amino acid residues, a combination of the amino acid residue replacements identified to contribute to the enhancement of the affinity based on the three-dimensional structure analysis of the

Escherichia blattae enzyme was introduced.

The mutations were introduced into the plasmid DNA by using Quick Change site-directed mutagenesis kit produced by Stratagene. Twenty kinds of oligonucleotides (Table 12) for introduction of mutation from MUT180 (SEQ ID NO: 101) to MUT521 (SEQ ID NO: 120) were synthesized by using a DNA synthesizer (Model 394 produced by Applied Biosystem). The mutations were introduced according to the protocol of Stratagene by using pENP170 as the first template and MUT180 and MUT181 as oligonucleotides for introduction of mutation.

Escherichia coli JM109 (produced by Takara Shuzo) was transformed with each obtained plasmid DNA in a conventional manner. The cells were plated on L agar medium containing 100 μg/ml of ampicillin to obtain transformants. A plasmid was prepared from the transformants by the alkali lysis method, and the nucleotide sequence was determined to confirm that the target nucleotide was replaced. The determination of the nucleotide sequence was performed according to the method of Sanger et al. (J. Mol. Biol., 143, 161 (1980)) using Taq DyeDeoxy Terminator Cycle Sequencing Kit (produced by Applied Biochemical). As described above, a gene coding for a mutant acid phosphatase was constructed, in which 153rd threonine residue (ACC) was replaced with a serine residue (TCC), and a plasmid containing this mutant gene was designated as pENP200.

By using a plasmid introduced with a mutation as a

new template, the same procedure was repeated to cumulatively introduce site-specific mutations. Plasmids were prepared from the transformants by the alkali lysis method, and their nucleotide sequences were determined to confirm that the target nucleotides were replaced. The prepared mutant enzyme genes coding for mutant acid phosphatases and the mutation sites thereof are shown in Table 13. The amino acid residues of the mutation sites represents the amino acid residues in the amino acid sequence shown in SEQ ID NO: 10.

Escherichia coli JM109/pENP180, *Escherichia coli* JM109/pENP320, *Escherichia coli* JM109/pENP340, *Escherichia coli* JM109/pENP410, *Escherichia coli* JM109/pENP510 and *Escherichia coli* JM109/pENP520, which were introduced with a plasmid containing each mutant acid phosphatase gene, were each inoculated to 50 ml of L medium containing 100 μg/ml of ampicillin and 1 mM of IPTG, and cultured at 37°C for 16 hours. The cells were suspended in 50 mL of 100 mM potassium phosphate buffer (pH 7.0), and disrupted by sonication at 4°C for 20 minutes. The cells were collected from each medium by centrifugation, and washed once with physiological saline. The insoluble fraction in the sonicated suspension was removed by centrifugation to prepare a cell free extract. Km values for inosine and guanosine in the transphosphorylation reaction were measured by using each cell free extract.

The measurement of the transphosphorylation

activity for a nucleoside was performed under the following conditions by using inosine and guanosine as substrates. The reaction was performed in a reaction mixture (1 ml) containing various concentrations of inosine or guanosine, 100 μmol/ml of sodium pyrophosphate, 100 μmol/ml of sodium acetate buffer solution (pH 4.0) and each enzyme at pH 4.0 and 30°C for 10 minutes. After the reaction was stopped by adding 200 μl of 2 N hydrochloric acid, the precipitates were removed by centrifugation, and 5′-inosinic acid or 5′-guanylic acid produced by the transphosphorylation reaction was quantified. Inosine, guanosine, 5′-inosinic acid and 5′-guanylic acid were analyzed by high performance liquid chromatography (HPLC) under the same conditions as Example 21.

The transphosphorylation activity was measured by changing the concentration of inosine or guanosine in the reaction conditions using the aforementioned composition, and rate constants of inosine and guanosine in the transphosphorylation reaction were determined by Hanes-Woolf plot (Biochem. J., 26, 1406 (1932)). The results are shown in Table 14. As for the Km values of the mutant enzymes produced in the examples, the Km values for guanosine markedly decreased, and thus it was revealed that the affinity for guanosine was improved. Moreover, the Km values for inosine were also markedly reduced in the four kinds of mutant enzymes other than the mutant enzyme encoded by pENP520.

Table 13

Plasmid	Plasmid introduced with mutation	Primer used for introduction of mutation	Mutation point and amino acid replacement
PENP180			61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC)
pENP200	pENP130	MUT180, MUT181	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151T(ACC)→S(TCC)
pENP300	pENP200	MUT300, MUT301	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP310	pENP300	MUT310, MUT311	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →V(GTT) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)

Table 13 (Cont.)

Plasmid	Plasmid introduced with mutation	Primer used for introduction of mutation	Mutation point and amino acid replacement
pENP320	pENP310	MUT320, MUT321	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →V(GTT) 72G(GGC) →D(GAC) 102E(GAG)→L(CTG) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP330	pENP300	MUT330, MUT331	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →M(ATG) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP340	pENP330	MUT340, MUT341	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →V(GTT) 72G(GGC) →D(GAC) 102E(GAG)→Q(CAG) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP400	pENP200	MUT400, MUT401	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→A(GCT) 151T(ACC)→S(TCC)

Table 13 (Cont.)

Plasmid	Plasmid introduced with mutation	Primer used for introduction of mutation	Mutation point and amino acid replacement
pENP410	pENP400	MUT310, MUT311	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →V(GTT) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→A(GCT) 151T(ACC)→S(TCC)
pENP500	pENP200	MUT500, MUT501	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)
pENP510	pENP500	MUT510, MUT511	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →E(GAA) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)
pENP520	pENP500	MUT520, MUT521	61L(CTG) →Q(CAG) 63A(GCT) →Q(CAG) 64E(GAA) →A(GCA) 67N(AAC) →D(GAC) 69S(AGC) →A(GCC) 70A(GCC) →K(AAA) 72G(GGC) →D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)

Table 14

	Km value for inosine (mM)	Relative activity when inosine is used as substrate	Km value for guanosine (mM)	Relative activity when guanosine is used as substrate
pENP180	40	1.0	40	1.0
pENP320	19	1.9	4.6	1.5
pENP340	19	1.4	5.1	1.3
pENP410	18	1.0	4.9	0.70
pENP510	17	0.55	4.0	0.39
pENP520	46	0.63	4.4	0.21

Example 23: Transphosphorylation reaction of guanosine by *E.coli* transformed with a plasmid containing gene for novel mutant acid phosphatase derived from *Enterobacter aerogenes* IFO12010 having improved affinity for guanosine

Escherichia coli JM109/pENP180, *Escherichia coli* JM109/pENP320, *Escherichia coli* JM109/pENP340, *Escherichia coli* JM109/pENP410, *Escherichia coli* JM109/pENP510 and *Escherichia coli* JM109/pENP520, which were transformed with a plasmid containing each mutant acid phosphatase gene, were inoculated to 50 ml of L medium containing 100 μg/ml of ampicillin and 1 mM of IPTG, and cultured at 37°C for 16 hours.

10 g/dl of pyrophosphoric acid and guanosine crystals were made into slurry in water, and subjected grinding treatment by a grinding mill (DYNO-MILL produced by WAB, Switzerland). 6.6 g/dl of the obtained guanosine was dissolved in 100 mM acetate buffer (pH 4.5), added with cells of each strain in an amount of

100 mg/dl in terms of dry cell weight, and allowed to react at 35°C for 12 hours while pH was maintained at 4.5. The amounts of produced 5′-guanylic acid are shown in Table 15. As shown in the table, all of the strains introduced with a mutant enzyme showed improved productivity compared with the parent strain, *Escherichia coli* JM109/pENP180, and produced and accumulated 5′-guanylic acid with high yield.

Table 15

Strain	Produced 5′-guanylic acid (g/dl)
Escherichia coli JM109/pENP180	9.90
Escherichia coli JM109/**pENP320**	10.4
Escherichia coli JM109/**pENP340**	10.2
Escherichia coli JM109/**pENP410**	11.1
Escherichia coli JM109/**pENP510**	11.0
Escherichia coli JM109/**pENP520**	10.5

Industrial Applicability

As explained above in detail, the present invention provides mutant nucleoside-5′-phosphate producing enzymes of which nucleoside-5′-phosphate producing ability is improved, and methods for producing them. The present invention further provides genes coding for the aforementioned mutant enzymes, recombinant DNA containing the genes and microorganisms that harbor the recombinant DNA, which are useful for a method for producing nucleoside-5′-phosphate.

Further, novel three-dimensional structures of

proteins were successfully elucidated by X-ray crystallography techniques.

The mutant nucleoside-5'-phosphate producing enzymes of the present invention can be used for the production of nucleoside-5'-phosphates useful as seasonings, drugs, raw materials therefor and so forth.

What is claimed is:

1. A mutant nucleoside-5′-phosphate producing enzyme with improved nucleoside-5′-phosphate producing ability, which is obtained by modifying a nucleoside-5′-phosphate producing enzyme that has transphosphorylation activity and/or phosphatase activity and has one Lys residue, two Arg residues and two His residues with distances between their Cα's within the ranges shown in Fig. 1 and a space around them allowing a binding of a nucleoside.

2. The mutant nucleoside-5′-phosphate producing enzyme according to claim 1, wherein the distances between Cα's of the Lys residue, two Arg residues and two His residues are within the ranges shown in Fig. 1.

3. The mutant nucleoside-5′-phosphate producing enzyme according to claim 1, wherein the nucleoside-5′-phosphate producing ability is improved by predicting a binding mode of the enzyme to a nucleoside such as inosine and guanosine and phosphorylated compounds thereof based on structural coordinates represented in the atomic coordinate data obtained by X-ray crystallographic analysis of acid phosphatase derived from *Escherichia blattae*, and substituting, adding or deleting at least one amino acid residue and/or a

prosthetic factor etc.

4. The mutant acid phosphatase according to claim 1, wherein the enzyme is derived from a bacterium belonging to the genus *Escherichia*, *Morganella*, *Providencia*, *Enterobacter* or *Klebsiella*.

5. A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has an amino acid sequence of the acid phosphatase derived from *Escherichia blattae* including modification at one or more of the following positions (Ser72 ~~of *Escherichia blattae* acid phosphatase~~ or residues located within a distance of 10Å from Ser72): 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 149-154, 157, 179 and 183.

6. A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions in the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* (Ser72 of *Escherichia blattae* acid phosphatase or residues located within a distance of 10Å from Ser72): 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 149-154, 157, 179 and 183

in amino acid sequence alignment with the acid phosphatase derived from *Escherichia blattae*.

7. A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions in the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* (Ser72 of *Escherichia blattae* acid phosphatase or residues located within a distance of 10Å from Ser72): 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 149-154, 157, 179 and 183 in alignment with the three-dimensional structure of the acid phosphatase derived from *Escherichia blattae* performed by the threading method.

8. The mutant nucleoside-5'-phosphate producing enzyme according to claim 6, wherein the three-dimensional structure of the enzyme is put close to that of an enzyme derived from another organism having transphosphorylation activity higher than that of a wild-type of the enzyme having the transphosphorylation activity and/or phosphatase activity by making modification at one or more positions other than the positions (Ser72 of *Escherichia blattae* acid phosphatase or residues present within a distance of 10Å from

Ser72).

9. A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has an amino acid sequence of the acid phosphatase derived from *Escherichia blattae* including modification at one or more of the following positions: 16, 71, 72, 73, 103, 104, 140, 151 and 153.

10. A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae*: 16, 71, 72, 73, 103, 104, 140, 151 and 153 in amino acid sequence alignment with the acid phosphatase derived from *Escherichia blattae*.

11. A mutant nucleoside-5'-phosphate producing enzyme with improved nucleoside-5'-phosphate producing ability, which has transphosphorylation activity and/or phosphatase activity, and has modification at one or more of positions corresponding to the following positions of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae*: 16, 71, 72,

73, 103, 104, 140, 151 and 153 in alignment with the three-dimensional structure of the acid phosphatase derived from *Escherichia blattae* performed by the threading method.

12. A mutant nucleoside-5'-phosphate producing enzyme, which has an amino acid sequence of the acid phosphatase derived from *Escherichia blattae* including replacement of the 72nd residue with another amino acid residue.

13. A mutant nucleoside-5'-phosphate producing enzyme, which has transphosphorylation activity and/or phosphatase activity, and has replacement of a residue corresponding to the 72nd residue of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* with another amino acid in amino acid sequence alignment with the acid phosphatase derived from *Escherichia blattae*.

14. A mutant nucleoside-5'-phosphate producing enzyme, which has transphosphorylation activity and/or phosphatase activity, and has replacement of a residue corresponding to the 72nd residue of the amino acid sequence of the acid phosphatase derived from *Escherichia blattae* with another amino acid in alignment with the three-dimensional structure of the acid

phosphatase derived from *Escherichia blattae* performed by the threading method.

15. The mutant acid phosphatase according to claim 10, wherein the enzyme is derived from *Enterobacter aerogenes*, and the amino acid sequence of the enzyme includes replacement with another amino acid residue of at least one amino acid residue among the 14th leucine residue, the 61st leucine residue, the 63rd alanine residue, the 64th glutamic acid residue, the 67th asparagine residue, the 69th serine residue, the 70th alanine residue, the 71st glycine residue, the 72nd glycine residue, the 101st isoleucine residue, the 102nd glutamic acid residue, the 133rd threonine residue, the 134th glutamic acid residue, the 138th leucine residue, 149th threonine residue and the 151st isoleucine residue.

16. The mutant acid phosphatase according to claim 12, wherein the enzyme is derived from *Enterobacter aerogenes*, and the enzyme has any one of following amino acid replacements:

(a) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th

alanine residue with a valine residue, the 72nd glycine residue with an aspartic acid residue, the 102nd glutamic acid residue with a leucine residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a serine residue and the 151st isoleucine residue with a serine residue;

(b) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a valine residue, the 72nd glycine residue with an aspartic acid residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a alanine residue and the 151st isoleucine residue with a serine residue;

(c) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a glutamic acid residue, the 72nd glycine residue with an aspartic acid residue, the 133rd

threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a glycine residue and the 151st isoleucine residue with a serine residue;

(d) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a lysine residue, the 72nd glycine residue with an aspartic acid residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the 149th threonine residue with a glycine residue and the 151st isoleucine residue with a serine residue; and

(e) mutation consisting of replacements of the 61st leucine residue with a glutamine residue, the 63rd alanine residue with a glutamine residue, the 64th glutamic acid residue with an alanine residue, the 67th asparagine residue with an aspartic acid residue, the 69th serine residue with an alanine residue, the 70th alanine residue with a methionine residue, the 72nd glycine residue with an aspartic acid residue, the 102nd glutamic acid residue with a glutamine residue, the 133rd threonine residue with a lysine residue, the 134th glutamic acid residue with an aspartic acid residue, the

149th threonine residue with a serine residue and the 151st isoleucine residue with a serine residue.

17. A method for producing a mutant nucleoside-5'-phosphate producing enzyme, wherein a mutant enzyme with improved nucleoside-5'-phosphate producing ability is produced by substituting, adding or deleting at least one amino acid residue in the active site of an enzyme having transphosphorylation activity and/or phosphatase activity and/or an amino acid residue located within a distance of 10Å from the active site, in which the active site is determined based on the three-dimensional structure of the enzyme obtained by X-ray crystallographic analysis of the enzyme or a complex of the enzyme with molybdate.

18. A method for producing an inhibitor for a phosphatase or transphosphorylation enzyme, which utilizes the atomic coordinates of the acid phosphatase derived from *Escherichia blattae*.

19. A crystal of an enzyme having transphosphorylation activity and/or phosphatase activity or the complex of the enzyme with molybdate.

20. A crystal of acid phosphatase derived from *Escherichia blattae*, which has a space group $P6_322$ of a

hexagonal system.

21. A crystal of mutant enzyme acid phosphatase G74D/I153T derived from *Escherichia blattae*, which has a space group $P2_12_12_1$ of a rhombic system.

22. A crystal of complex of acid phosphatase derived from *Escherichia blattae* and molybdate (reaction intermediate analogue), which has a space group $P3_121$ of a trigonal system.

23. A gene coding for any one of the enzymes according to any one of claims 1-16.

24. A recombinant DNA, which contains the gene according to claim 23.

25. A microorganism, which contains the gene according to claim 23 or the recombinant DNA according to claim 24.

26. A method for producing a nucleoside-5′-phosphate, which comprises allowing the enzyme according to any one of claims 1-16, a microorganism containing it or the microorganism according to claim 25 to act on a nucleoside and a phosphate donor to produce nucleoside-5′-phosphate and collecting it.

27. The method according to claim 26, wherein the enzyme, the microorganism containing it or the microorganism according to claim 25 is allowed to act on a nucleoside and a phosphate donor under a condition of pH 3.0-5.5.

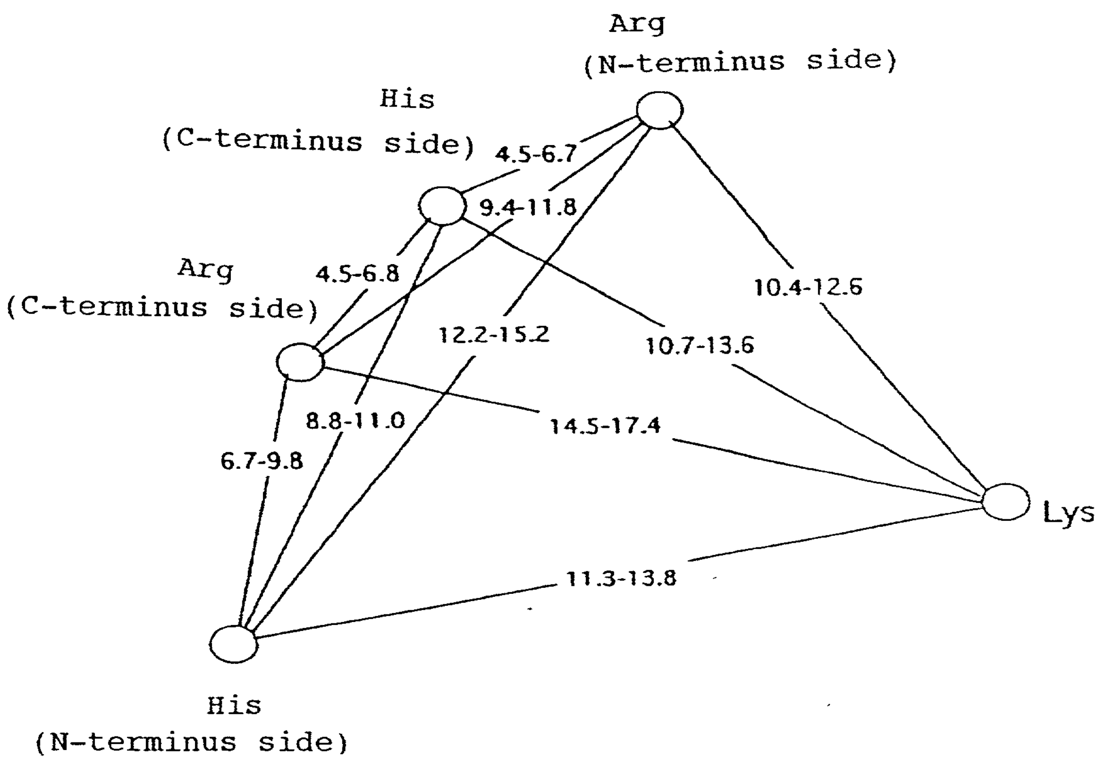
Arg
(N-terminus side)
His
(C-terminus side)
4.5-6.7
9.4-11.8
Arg
(C-terminus side)
4.5-6.8
10.4-12.6
12.2-15.2
10.7-13.6
8.8-11.0
14.5-17.4
6.7-9.8
Lys
11.3-13.8
His
(N-terminus side)

FIG. 1

```
                                                α1                      α2                    α3
E.blattae      :LALVATGNDT TTKPDLYYLK NSEAINSLAL LPPPPAVGSI AFLNDQAMYE QGRLLRNTER GKLAAEDANL  70
M.morganii     :  AIPAGNDA TTKPDLYYLK NEQAIDSLKL LPPPPEVGSI QFLNDQAMYE KGRMLRNTER GKQAQADADL
S.typhimurium  :       KYT SAETVQPFHS PEESVNSQFY LPPPPGNDDP AYRYDKEAYF KGYAILGSPR WKQAAEDADV
Z.mobilis      :ASGLSQSVSA HTEKSEPSST YHFHSDPLLY LAPPPTSGSP LQAHDDQTFN STRQLKGSTR WALATQDADL
                                              * ***          *              *     *   **

           α4      α5               α6       α7          α8        α9
E.blattae      :SSGGVANAFS GAFGSPITEK DAPALHKLLT NMIEDAGDLA TRSAKDHYMR IRPFAFYGVS TCNTTEQDKL  140
M.morganii     :AAGGVATAFS GAFGYPITEK DSPELYKLLT NMIEDAGDLA TRSAKEHYMR IRPFAFYGTE TCNTKDQKKL
S.typhimurium  :SVENIARIFS PVVGAKINPK DTPETWNMLK NLLTMGGYYA TASAKKYYMR TRPFVLFNHS TCRPEDENTL
Z.mobilis      :HLASVLKDYA CAAGMNLDIA QLPHLANLIK RALRTEYDDI GR-AKNNWNR KRPFVDTDQP ICTEKDREGL
                           *          *                       **    *  ***        *      *

                          α10                  α11                   α12
E.blattae      :SKNGSYPSGH TSIGWATALV LAEINPQRQN EILKRGYELG QSRVICGYHW QSDVDAARVV GSAVVATLHT  210
M.morganii     :STNGSYPSGH TSIGWATALV LAEVNPANQD AILERGYQLG QSRVICGYHW QSDVDAARIV GSAAVATLHS
S.typhimurium  :RKNGSYPSGH TAYGTLLALV LSEARPERAQ ELARRGWEFG QSRVICGAHW QSDVDAGRYV GAVEFARLQT
Z.mobilis      :GKQGSYPSGH TTIGWSVALI LAELIPDHAA NILQRGQIFG TSRIVCGAHW FSDVQAGYIM ASGEIAALHG
                   ******* *  *   **  * *  *        **   *  **  ** **  *** *         * *

                 α13
E.blattae      :NPAFQQQLQK AKAEFAQHQK K
M.morganii     :DPAFQAQLAK AKQEFAQKSQ K
S.typhimurium  :IPAFQKSLAK VREELNDKNN LLSKEDHPKL NY
Z.mobilis      :DADFRRDMEL ARKELEKART SAHTPDDLLC KIEQSAR
                 *          *
```

FIG. 2

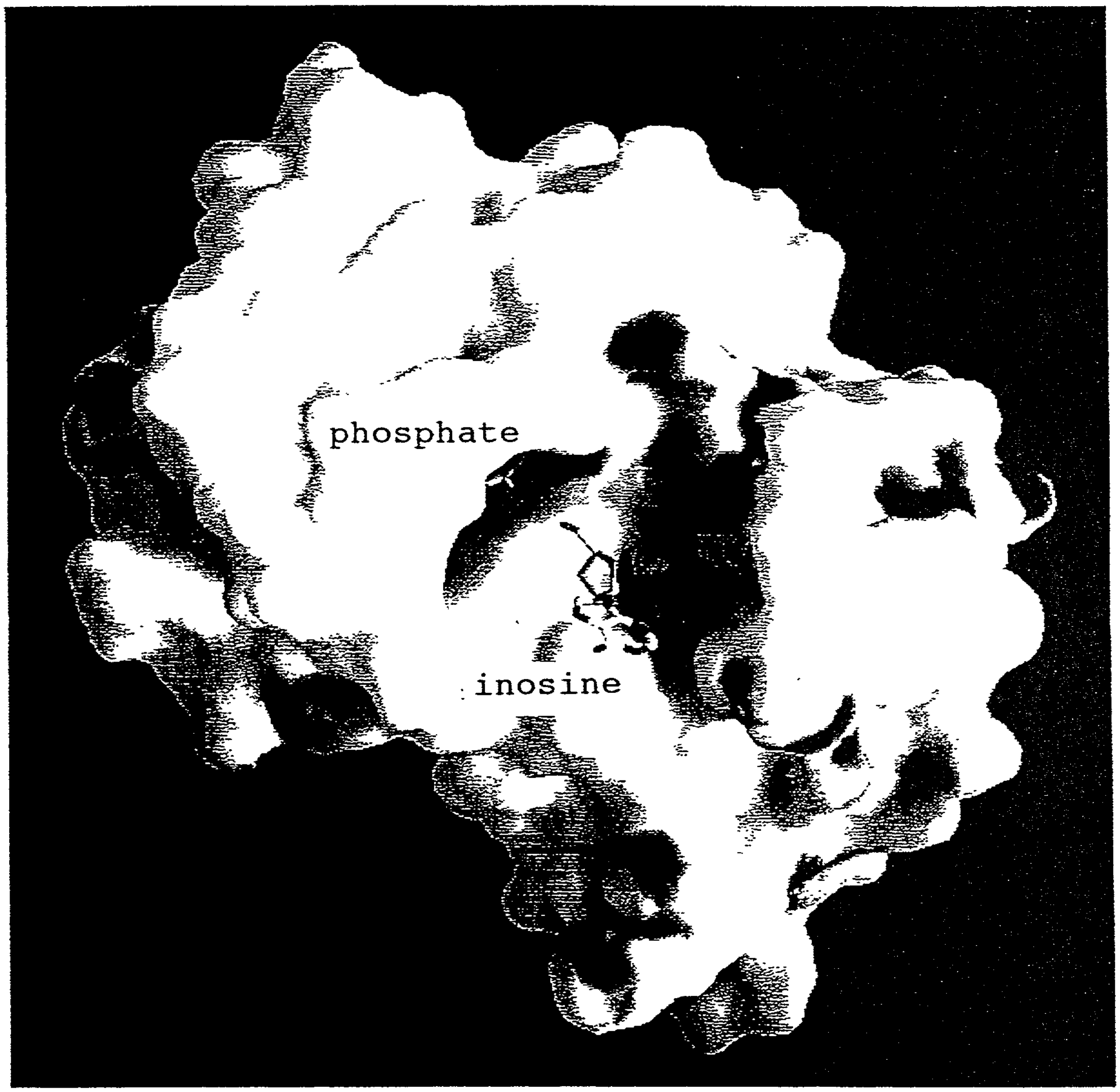

FIG. 3

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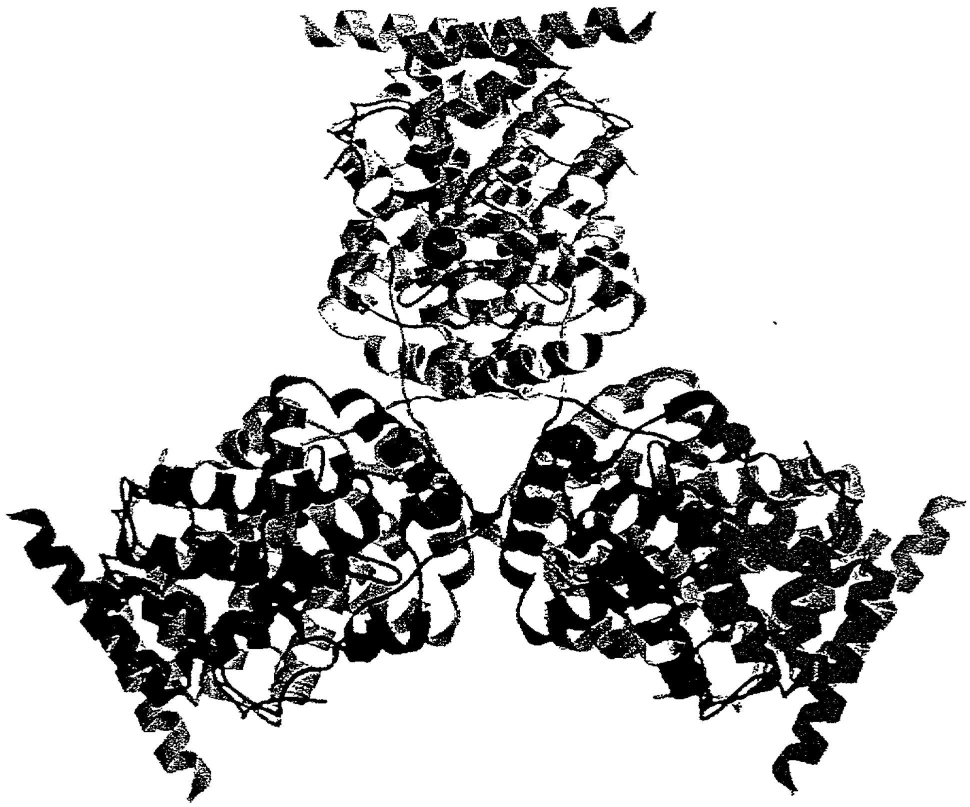
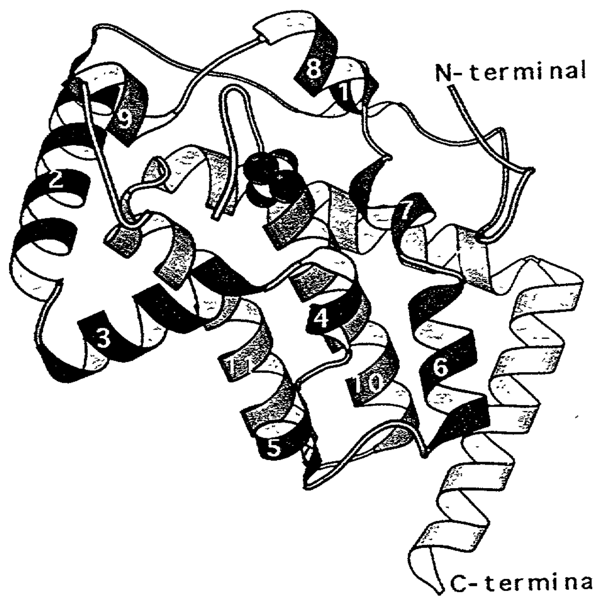
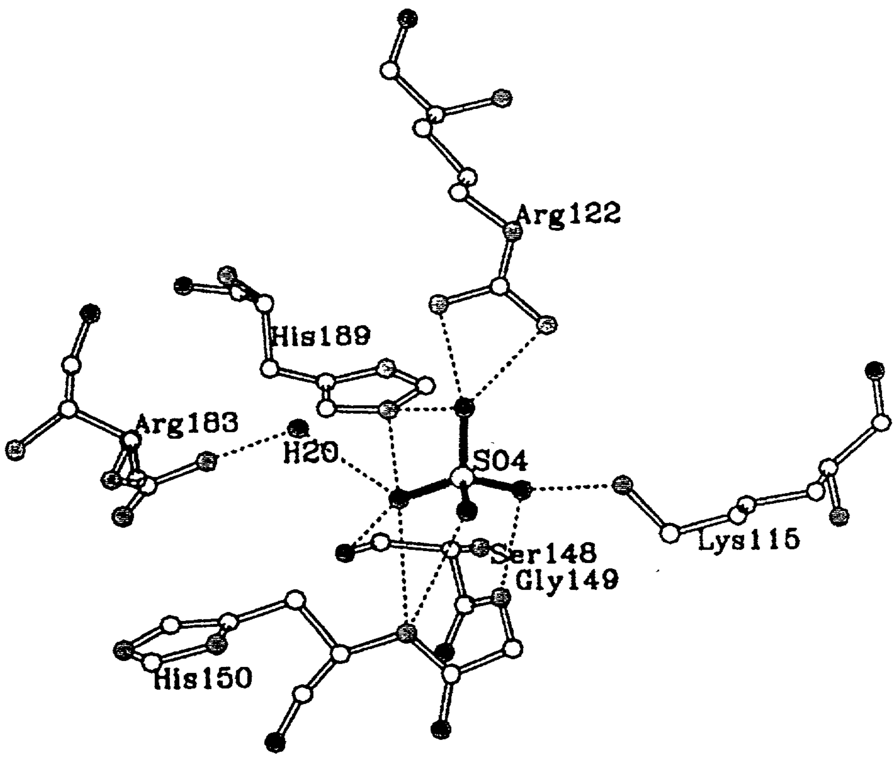


F I G. 4



F I G. 5



F I G. 6

F I G. 7

S72F(s)	5'-CA-AAC-CTG-AGC-TTT-GGC-GAT-GTG-GC-3'	(SEQ ID NO:11)
S72F(as)	3'-GT-TTG-GAC-TCG-AAA-CCG-CTA-CAC-CG-5'	(SEQ ID NO:12)
	N L S F72 G D V	(SEQ ID NO:13)
S72Y(s)	5'-CA-AAC-CTG-AGC-TAC-GGC-GAT-GTG-GC-3'	(SEQ ID NO:14)
S72Y(as)	3'-GT-TTG-GAC-TCG-ATG-CCG-CTA-CAC-CG-5'	(SEQ ID NO:15)
	N L S Y72 G D V	(SEQ ID NO:16)
S72W(s)	5'-CA-AAC-CTG-AGC-TGG-GGC-GAT-GTG-GC-3'	(SEQ ID NO:17)
S72W(as)	3'-GT-TTG-GAC-TCG-ACC-CCG-CTA-CAC-CG-5'	(SEQ ID NO:18)
	N L S W72 G D V	(SEQ ID NO:19)
S72D(s)	5'-CA-AAC-CTG-AGC-GAC-GGC-GAT-GTG-GC-3'	(SEQ ID NO:20)
S72D(as)	3'-GT-TTG-GAC-TCG-CTG-CCG-CTA-CAC-CG-5'	(SEQ ID NO:21)
	N L S D72 G D V	(SEQ ID NO:22)
S72V(s)	5'-CA-AAC-CTG-AGC-GTT-GGC-GAT-GTG-GC-3'	(SEQ ID NO:23)
S72V(as)	3'-GT-TTG-GAC-TCG-CAA-CCG-CTA-CAC-CG-5'	(SEQ ID NO:24)
	N L S V72 G D V	(SEQ ID NO:25)
S72E(s)	5'-CA-AAC-CTG-AGC-GAA-GGC-GAT-GTG-GC-3'	(SEQ ID NO:26)
S72E(as)	3'-GT-TTG-GAC-TCG-CTT-CCG-CTA-CAC-CG-5'	(SEQ ID NO:27)
	N L S E72 G D V	(SEQ ID NO:28)
S72M(s)	5'-CA-AAC-CTG-AGC-ATG-GGC-GAT-GTG-GC-3'	(SEQ ID NO:29)
S72M(as)	3'-GT-TTG-GAC-TCG-TAC-CCG-CTA-CAC-CG-5'	(SEQ ID NO:30)
	N L S M72 G D V	(SEQ ID NO:31)
S72T(s)	5'-CA-AAC-CTG-AGC-ACC-GGC-GAT-GTG-GC-3'	(SEQ ID NO:32)
S72T(as)	3'-GT-TTG-GAC-TCG-TGG-CCG-CTA-CAC-CG-5'	(SEQ ID NO:33)
	N L S T72 G D V	(SEQ ID NO:34)
S72L(s)	5'-CA-AAC-CTG-AGC-CTG-GGC-GAT-GTG-GC-3'	(SEQ ID NO:35)
S72L(as)	3'-GT-TTG-GAC-TCG-GAC-CCG-CTA-CAC-CG-5'	(SEQ ID NO:36)
	N L S L72 G D V	(SEQ ID NO:37)
S72R(s)	5'-CA-AAC-CTG-AGC-CGT-GGC-GAT-GTG-GC-3'	(SEQ ID NO:38)
S72R(as)	3'-GT-TTG-GAC-TCG-GCA-CCG-CTA-CAC-CG-5'	(SEQ ID NO:39)
	N L S R72 G D V	(SEQ ID NO:40)
S72Q(s)	5'-CA-AAC-CTG-AGC-CAG-GGC-GAT-GTG-GC-3'	(SEQ ID NO:41)
S72Q(as)	3'-GT-TTG-GAC-TCG-GTC-CCG-CTA-CAC-CG-5'	(SEQ ID NO:42)
	N L S Q72 G D V	(SEQ ID NO:43)

S72K(s)	5'-CA-AAC-CTG-AGC-AAA-GGC-GAT-GTG-GC-3'	(SEQ ID NO:44)
S72K(as)	3'-GT-TTG-GAC-TCG-TTT-CCG-CTA-CAC-CG-5'	(SEQ ID NO:45)
	N L S K72 G D V	(SEQ ID NO:46)
S72P(s)	5'-CA-AAC-CTG-AGC-CCG-GGC-GAT-GTG-GC-3'	(SEQ ID NO:47)
S72P(as)	3'-GT-TTG-GAC-TCG-GGC-CCG-CTA-CAC-CG-5'	(SEQ ID NO:48)
	N L S P72 G D V	(SEQ ID NO:49)
S72A(s)	5'-CA-AAC-CTG-AGC-GCG-GGC-GAT-GTG-GC-3'	(SEQ ID NO:50)
S72A(as)	3'-GT-TTG-GAC-TCG-CGC-CCG-CTA-CAC-CG-5'	(SEQ ID NO:51)
	N L S A72 G D V	(SEQ ID NO:52)
S72N(s)	5'-CA-AAC-CTG-AGC-AAC-GGC-GAT-GTG-GC-3'	(SEQ ID NO:53)
S72N(as)	3'-GT-TTG-GAC-TCG-TTG-CCG-CTA-CAC-CG-5'	(SEQ ID NO:54)
	N L S N72 G D V	(SEQ ID NO:55)
S72G(s)	5'-CA-AAC-CTG-AGC-GGT-GGC-GAT-GTG-GC-3'	(SEQ ID NO:56)
S72G(as)	3'-GT-TTG-GAC-TCG-CCA-CCG-CTA-CAC-CG-5'	(SEQ ID NO:57)
	N L S G72 G D V	(SEQ ID NO:58)
S72H(s)	5'-CA-AAC-CTG-AGC-CAC-GGC-GAT-GTG-GC-3'	(SEQ ID NO:59)
S72H(as)	3'-GT-TTG-GAC-TCG-GTG-CCG-CTA-CAC-CG-5'	(SEQ ID NO:60)
	N L S H72 G D V	(SEQ ID NO:61)

F I G. 7

L16W(s)	5'-CG-AAA-CCG-GAT-TGG-TAC-TAC-CTC-AA-3'	(SEQ ID NO:62)
L16W(as)	3'-GC-TTT-GGC-CTA-ACC-ATG-ATG-GAG-TT-5'	(SEQ ID NO:63)
	K P D W16 Y Y L	(SEQ ID NO:64)
S71W(s)	5'-AT-GCA-AAC-CTG-TGG-AGT-GGC-GAT-GT-3'	(SEQ ID NO:65)
S71W(as)	3'-TA-CGT-TTG-GAC-ACC-TCA-CCG-CTA-CA-5'	(SEQ ID NO:66)
	A N L W71 S G D	(SEQ ID NO:67)
S73W(s)	5'-AC-CTG-AGC-AGT-TGG-GAT-GTG-GCG-AA-3'	(SEQ ID NO:68)
S73W(as)	3'-TG-GAC-TCG-TCA-ACC-CTA-CAC-CGC-TT-5'	(SEQ ID NO:69)
	L S S W73 D V A	(SEQ ID NO:70)
E104F(s)	5'-CC-AAT-ATG-ATT-TTT-GAC-GCC-GGG-GA-3'	(SEQ ID NO:71)
E104F(as)	3'-GG-TTA-TAC-TAA-AAA-CTG-CGG-CCC-CT-5'	(SEQ ID NO:72)
	N M I F104 D A G	(SEQ ID NO:73)
E104W(s)	5'-CC-AAT-ATG-ATT-TGG-GAC-GCC-GGG-GA-3'	(SEQ ID NO:74)
E104W(as)	3'-GG-TTA-TAC-TAA-ACC-CTG-CGG-CCC-CT-5'	(SEQ ID NO:75)
	N M I W104 D A G	(SEQ ID NO:76)

FIG. 8A

A72F(s)	5'-CA-GAC-CTG-GCC-TTT-GGC-GAT-GTG-GC-3'	(SEQ ID NO:77)
A72F(as)	3'-GT-CTG-GAC-CGG-AAA-CCG-CTA-CAC-CG-5'	(SEQ ID NO:78)
	D L A F72 G D V	(SEQ ID NO:79)
A72E(s)	5'-CA-GAC-CTG-GCC-GAA-GGC-GAT-GTG-GC-3'	(SEQ ID NO:80)
A72E(as)	3'-GT-CTG-GAC-CGG-CTT-CCG-CTA-CAC-CG-5'	(SEQ ID NO:81)
	D L A E72 G D V	(SEQ ID NO:82)

F I G. 8 B

I103D(s)	5'-TG-ACC-AAT-ATG-GAC-GAG-GAC-GCC-GG-3'	(SEQ ID NO:83)
I103D(as)	3'-AC-TGG-TTA-TAC-CTG-CTC-CTG-CGG-CC-5'	(SEQ ID NO:84)
	T N M D103 E D A	(SEQ ID NO:85)
T153N(s)	5'-GG-CAT-ACC-TCT-AAC-GGC-TGG-GCT-AC-3'	(SEQ ID NO:86)
T153N(as)	3'-CC-GTA-TGG-AGA-TTG-CCG-ACC-CGA-TG-5'	(SEQ ID NO:87)
	H T S N153 G W A	(SEQ ID NO:88)

F I G. 8 C

L140F(s)	5'-AC-CAG-GAC-AAA-TTC-TCC-AAA-AAT-GG-3'	(SEQ ID NO:89)
L140F(as)	3'-TG-GTC-CTG-TTT-AAG-AGG-TTT-TTA-CC-5'	(SEQ ID NO:90)
	Q D K F140 S K N	(SEQ ID NO:91)
L140K(s)	5'-AC-CAG-GAC-AAA-AAA-TCC-AAA-AAT-GG-3'	(SEQ ID NO:92)
L140K(as)	3'-TG-GTC-CTG-TTT-TTT-AGG-TTT-TTA-CC-5'	(SEQ ID NO:93)
	Q D K K140 S K N	(SEQ ID NO:94)
L140E(s)	5'-AC-CAG-GAC-AAA-GAA-TCC-AAA-AAT-GG-3'	(SEQ ID NO:95)
L140E(as)	3'-TG-GTC-CTG-TTT-CTT-AGG-TTT-TTA-CC-5'	(SEQ ID NO:96)
	Q D K E140 S K N	(SEQ ID NO:97)

F I G. 8 D

```
EB-AP:   LALVATGNDTTTKPDLYYLKNSEAINSLALLPPPPAVGSIAFLNDQAMYEQGRLLRNTER
            V  GND TTKPDLYYLKN++AI+SLALLPPPP VGSIAFLNDQAMYE+GRLLRNTER
EA-AP:     LVPAGNDATTKPDLYYLKNAQAIDSLALLPPPPEVGSIAFLNDQAMYEKGRLLRNTER

                       [72]
EB-AP:   GKLAAEDANLSSGGVANAFSGAFGSPITEKDAPALHKLLTNMIEDAGDLATRSAKDHYMR
         GKLAAEDANLS+GGVANAFS AFGSPITEKDAP LHKLLTNMIEDAGDLATRSAK+ YMR
EA-AP:   GKLAAEDANLSAGGVANAFSSAFGSPITEKDAPQLHKLLTNMIEDAGDLATRSAKEKYMR
                       [70]

EB-AP:   IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAEINPQRQNEILKRGYELG
         IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAEINPQRQNEILKRGYELG
EA-AP:   IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAEINPQRQNEILKRGYELG

EB-AP:   QSRVICGYHWQSDVDAARVVGSAVVATLHTNPAFQQQLQKAKAEFAQHQKK
         +SRVICGYHWQSDVDAAR+VGSAVVATLHTNPAFQQQLQKAK EFA+ QK
EA-AP:   ESRVICGYHWQSDVDAARIVGSAVVATLHTNPAFQQQLQKAKDEFAKTQK
```

FIG. 9

FIG. 10

ATOM	1	N	GLY	A	7	35.965	71.208	89.712	1.00	36.57
ATOM	2	CA	GLY	A	7	37.459	71.295	89.574	1.00	31.92
ATOM	3	C	GLY	A	7	38.160	69.982	89.872	1.00	29.76
ATOM	4	O	GLY	A	7	39.301	69.858	89.492	1.00	31.81
ATOM	5	N	ASN	A	8	37.485	68.990	90.532	1.00	26.40
ATOM	6	CA	ASN	A	8	38.284	67.775	90.697	1.00	26.63
ATOM	7	C	ASN	A	8	38.466	67.018	89.396	1.00	29.21
ATOM	8	O	ASN	A	8	37.736	67.238	88.431	1.00	30.52
ATOM	9	CB	ASN	A	8	37.677	66.810	91.702	1.00	27.01
ATOM	10	CG	ASN	A	8	37.725	67.396	93.104	1.00	32.45
ATOM	11	OD1	ASN	A	8	38.751	67.744	93.636	1.00	30.02
ATOM	12	ND2	ASN	A	8	36.545	67.536	93.707	1.00	31.60
ATOM	13	N	ASP	A	9	39.455	66.154	89.463	1.00	29.14
ATOM	14	CA	ASP	A	9	39.787	65.216	88.391	1.00	30.47
ATOM	15	C	ASP	A	9	40.661	64.081	88.901	1.00	31.02
ATOM	16	O	ASP	A	9	40.804	63.931	90.110	1.00	31.00
ATOM	17	CB	ASP	A	9	40.394	65.960	87.195	1.00	30.92
ATOM	18	CG	ASP	A	9	41.802	66.484	87.429	1.00	32.66
ATOM	19	OD1	ASP	A	9	42.307	66.333	88.532	1.00	35.03
ATOM	20	OD2	ASP	A	9	42.400	67.018	86.493	1.00	31.63
ATOM	21	N	THR	A	10	41.272	63.298	87.998	1.00	28.72
ATOM	22	CA	THR	A	10	42.188	62.228	88.430	1.00	28.53
ATOM	23	C	THR	A	10	43.408	62.655	89.259	1.00	30.10
ATOM	24	O	THR	A	10	43.946	61.944	90.095	1.00	29.06
ATOM	25	CB	THR	A	10	42.692	61.405	87.235	1.00	26.05
ATOM	26	OG1	THR	A	10	43.272	60.172	87.655	1.00	27.75
ATOM	27	CG2	THR	A	10	43.670	62.174	86.313	1.00	23.76
ATOM	28	N	THR	A	11	43.814	63.900	88.996	1.00	30.82
ATOM	29	CA	THR	A	11	44.932	64.389	89.799	1.00	32.79
ATOM	30	C	THR	A	11	44.605	64.736	91.267	1.00	36.32
ATOM	31	O	THR	A	11	45.435	64.658	92.162	1.00	37.21
ATOM	32	CB	THR	A	11	45.588	65.591	89.143	1.00	30.53
ATOM	33	OG1	THR	A	11	44.845	66.781	89.359	1.00	27.79
ATOM	34	CG2	THR	A	11	45.899	65.362	87.656	1.00	32.16
ATOM	35	N	THR	A	12	43.317	65.076	91.495	1.00	34.81
ATOM	36	CA	THR	A	12	42.910	65.213	92.900	1.00	32.91
ATOM	37	C	THR	A	12	42.265	63.992	93.549	1.00	33.08
ATOM	38	O	THR	A	12	42.350	63.742	94.736	1.00	32.49
ATOM	39	CB	THR	A	12	41.963	66.395	93.077	1.00	30.92
ATOM	40	OG1	THR	A	12	40.719	66.162	92.409	1.00	32.04
ATOM	41	CG2	THR	A	12	42.599	67.667	92.543	1.00	29.75
ATOM	42	N	LYS	A	13	41.565	63.229	92.703	1.00	31.17
ATOM	43	CA	LYS	A	13	40.791	62.064	93.174	1.00	30.27
ATOM	44	C	LYS	A	13	40.904	60.812	92.287	1.00	31.40
ATOM	45	O	LYS	A	13	39.981	60.348	91.605	1.00	33.05
ATOM	46	CB	LYS	A	13	39.294	62.395	93.331	1.00	29.09
ATOM	47	CG	LYS	A	13	39.001	63.747	93.965	1.00	32.97
ATOM	48	CD	LYS	A	13	37.536	64.076	94.166	1.00	37.86
ATOM	49	CE	LYS	A	13	36.767	62.909	94.772	1.00	47.28
ATOM	50	NZ	LYS	A	13	35.340	63.270	94.947	1.00	52.08
ATOM	51	N	PRO	A	14	42.138	60.283	92.279	1.00	33.01
ATOM	52	CA	PRO	A	14	42.516	59.249	91.290	1.00	32.06
ATOM	53	C	PRO	A	14	41.823	57.907	91.452	1.00	30.98
ATOM	54	O	PRO	A	14	41.961	56.989	90.668	1.00	32.57

FIG. 11

ATOM	55	CB	PRO	A	14	44.035	59.145	91.468	1.00	34.46
ATOM	56	CG	PRO	A	14	44.283	59.564	92.920	1.00	33.02
ATOM	57	CD	PRO	A	14	43.225	60.638	93.181	1.00	34.46
ATOM	58	N	ASP	A	15	41.046	57.815	92.513	1.00	29.27
ATOM	59	CA	ASP	A	15	40.204	56.655	92.809	1.00	28.89
ATOM	60	C	ASP	A	15	38.810	56.684	92.146	1.00	21.76
ATOM	61	O	ASP	A	15	38.078	55.706	92.030	1.00	20.59
ATOM	62	CB	ASP	A	15	40.125	56.599	94.368	1.00	37.60
ATOM	63	CG	ASP	A	15	39.589	57.903	95.080	1.00	45.11
ATOM	64	OD1	ASP	A	15	40.062	59.044	94.817	1.00	45.67
ATOM	65	OD2	ASP	A	15	38.687	57.751	95.922	1.00	49.07
ATOM	66	N	LEU	A	16	38.495	57.910	91.726	1.00	20.49
ATOM	67	CA	LEU	A	16	37.182	58.179	91.135	1.00	23.90
ATOM	68	C	LEU	A	16	37.156	58.814	89.727	1.00	22.23
ATOM	69	O	LEU	A	16	36.109	59.011	89.134	1.00	23.21
ATOM	70	CB	LEU	A	16	36.354	59.099	92.029	1.00	23.35
ATOM	71	CG	LEU	A	16	35.814	58.432	93.297	1.00	25.48
ATOM	72	CD1	LEU	A	16	34.876	57.253	93.075	1.00	24.05
ATOM	73	CD2	LEU	A	16	35.092	59.477	94.104	1.00	25.22
ATOM	74	N	TYR	A	17	38.343	59.175	89.273	1.00	20.96
ATOM	75	CA	TYR	A	17	38.555	59.605	87.889	1.00	22.04
ATOM	76	C	TYR	A	17	39.780	58.903	87.334	1.00	22.80
ATOM	77	O	TYR	A	17	40.790	58.799	88.021	1.00	23.48
ATOM	78	CB	TYR	A	17	38.856	61.095	87.711	1.00	18.01
ATOM	79	CG	TYR	A	17	37.928	62.099	88.371	1.00	24.78
ATOM	80	CD1	TYR	A	17	37.129	62.916	87.542	1.00	22.78
ATOM	81	CD2	TYR	A	17	37.905	62.248	89.781	1.00	23.58
ATOM	82	CE1	TYR	A	17	36.317	63.919	88.113	1.00	26.51
ATOM	83	CE2	TYR	A	17	37.090	63.240	90.349	1.00	22.88
ATOM	84	CZ	TYR	A	17	36.303	64.059	89.517	1.00	24.63
ATOM	85	OH	TYR	A	17	35.482	65.023	90.066	1.00	22.92
ATOM	86	N	TYR	A	18	39.670	58.482	86.053	1.00	26.17
ATOM	87	CA	TYR	A	18	40.838	58.209	85.191	1.00	21.13
ATOM	88	C	TYR	A	18	41.332	59.414	84.464	1.00	19.92
ATOM	89	O	TYR	A	18	42.490	59.511	84.083	1.00	22.64
ATOM	90	CB	TYR	A	18	40.563	57.195	84.080	1.00	17.53
ATOM	91	CG	TYR	A	18	40.312	55.826	84.610	1.00	16.91
ATOM	92	CD1	TYR	A	18	41.425	55.028	84.916	1.00	19.86
ATOM	93	CD2	TYR	A	18	38.985	55.372	84.771	1.00	16.65
ATOM	94	CE1	TYR	A	18	41.218	53.725	85.383	1.00	18.64
ATOM	95	CE2	TYR	A	18	38.765	54.053	85.213	1.00	17.52
ATOM	96	CZ	TYR	A	18	39.892	53.262	85.515	1.00	21.18
ATOM	97	OH	TYR	A	18	39.734	51.974	85.977	1.00	26.15
ATOM	98	N	LEU	A	19	40.412	60.336	84.236	1.00	21.49
ATOM	99	CA	LEU	A	19	40.788	61.462	83.366	1.00	22.71
ATOM	100	C	LEU	A	19	41.094	62.812	84.021	1.00	25.01
ATOM	101	O	LEU	A	19	40.771	63.125	85.159	1.00	25.24
ATOM	102	CB	LEU	A	19	39.708	61.669	82.290	1.00	21.68
ATOM	103	CG	LEU	A	19	39.301	60.442	81.432	1.00	22.88
ATOM	104	CD1	LEU	A	19	40.430	59.842	80.583	1.00	20.39
ATOM	105	CD2	LEU	A	19	38.078	60.812	80.608	1.00	18.83
ATOM	106	N	LYS	A	20	41.736	63.667	83.246	1.00	26.44
ATOM	107	CA	LYS	A	20	41.947	65.032	83.717	1.00	26.77
ATOM	108	C	LYS	A	20	40.935	66.034	83.292	1.00	26.42

FIG. 12

ATOM	109	O	LYS	A	20	40.182	65.870	82.341	1.00	29.05
ATOM	110	CB	LYS	A	20	43.239	65.608	83.187	1.00	30.61
ATOM	111	CG	LYS	A	20	44.400	64.791	83.648	1.00	32.90
ATOM	112	CD	LYS	A	20	45.633	65.326	82.963	1.00	39.72
ATOM	113	CE	LYS	A	20	46.698	64.259	83.113	1.00	50.27
ATOM	114	NZ	LYS	A	20	46.148	62.977	82.610	1.00	62.00
ATOM	115	N	ASN	A	21	41.050	67.184	83.943	1.00	24.09
ATOM	116	CA	ASN	A	21	40.154	68.246	83.530	1.00	23.98
ATOM	117	C	ASN	A	21	40.177	68.539	82.032	1.00	25.08
ATOM	118	O	ASN	A	21	39.134	68.722	81.427	1.00	25.36
ATOM	119	CB	ASN	A	21	40.310	69.512	84.371	1.00	23.81
ATOM	120	CG	ASN	A	21	39.601	69.311	85.697	1.00	26.97
ATOM	121	OD1	ASN	A	21	38.392	69.175	85.836	1.00	26.36
ATOM	122	ND2	ASN	A	21	40.403	69.303	86.744	1.00	32.00
ATOM	123	N	SER	A	22	41.378	68.486	81.450	1.00	23.72
ATOM	124	CA	SER	A	22	41.592	68.804	80.008	1.00	25.53
ATOM	125	C	SER	A	22	40.992	67.752	79.068	1.00	25.77
ATOM	126	O	SER	A	22	40.524	68.007	77.966	1.00	27.65
ATOM	127	CB	SER	A	22	43.079	68.868	79.699	1.00	23.34
ATOM	128	OG	SER	A	22	43.719	67.716	80.303	1.00	33.30
ATOM	129	N	GLU	A	23	40.957	66.529	79.624	1.00	22.35
ATOM	130	CA	GLU	A	23	40.320	65.466	78.899	1.00	21.87
ATOM	131	C	GLU	A	23	38.811	65.375	78.974	1.00	23.18
ATOM	132	O	GLU	A	23	38.197	64.451	78.471	1.00	25.83
ATOM	133	CB	GLU	A	23	40.923	64.165	79.337	1.00	22.13
ATOM	134	CG	GLU	A	23	42.451	64.215	79.214	1.00	26.78
ATOM	135	CD	GLU	A	23	43.021	62.908	79.718	1.00	30.40
ATOM	136	OE1	GLU	A	23	42.946	62.648	80.900	1.00	31.10
ATOM	137	OE2	GLU	A	23	43.544	62.118	78.957	1.00	32.35
ATOM	138	N	ALA	A	24	38.196	66.359	79.610	1.00	21.49
ATOM	139	CA	ALA	A	24	36.751	66.165	79.738	1.00	22.48
ATOM	140	C	ALA	A	24	35.973	66.420	78.438	1.00	22.81
ATOM	141	O	ALA	A	24	36.325	67.333	77.704	1.00	23.36
ATOM	142	CB	ALA	A	24	36.188	67.183	80.734	1.00	21.43
ATOM	143	N	ILE	A	25	34.859	65.694	78.228	1.00	23.46
ATOM	144	CA	ILE	A	25	33.845	66.149	77.243	1.00	23.60
ATOM	145	C	ILE	A	25	33.312	67.535	77.530	1.00	24.71
ATOM	146	O	ILE	A	25	32.788	67.809	78.603	1.00	25.03
ATOM	147	CB	ILE	A	25	32.684	65.160	77.096	1.00	20.26
ATOM	148	CG1	ILE	A	25	33.237	63.749	76.838	1.00	23.14
ATOM	149	CG2	ILE	A	25	31.739	65.555	75.954	1.00	21.26
ATOM	150	CD1	ILE	A	25	34.298	63.551	75.722	1.00	16.94
ATOM	151	N	ASN	A	26	33.485	68.431	76.562	1.00	22.50
ATOM	152	CA	ASN	A	26	32.797	69.706	76.751	1.00	22.04
ATOM	153	C	ASN	A	26	31.295	69.680	76.533	1.00	22.52
ATOM	154	O	ASN	A	26	30.731	70.042	75.509	1.00	22.34
ATOM	155	CB	ASN	A	26	33.474	70.744	75.900	1.00	20.15
ATOM	156	CG	ASN	A	26	32.982	72.133	76.217	1.00	24.94
ATOM	157	OD1	ASN	A	26	31.923	72.459	76.732	1.00	29.46
ATOM	158	ND2	ASN	A	26	33.827	73.032	75.809	1.00	25.76
ATOM	159	N	SER	A	27	30.627	69.289	77.622	1.00	19.77
ATOM	160	CA	SER	A	27	29.166	69.168	77.549	1.00	18.88
ATOM	161	C	SER	A	27	28.412	70.423	77.177	1.00	18.74
ATOM	162	O	SER	A	27	27.390	70.393	76.517	1.00	21.73

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FIG. 13

ATOM	163	CB	SER	A	27	28.606	68.619	78.870	1.00	19.35
ATOM	164	OG	SER	A	27	28.967	69.518	79.940	1.00	19.36
ATOM	165	N	LEU	A	28	28.961	71.564	77.588	1.00	18.08
ATOM	166	CA	LEU	A	28	28.271	72.815	77.262	1.00	20.15
ATOM	167	C	LEU	A	28	28.283	73.062	75.761	1.00	23.12
ATOM	168	O	LEU	A	28	27.303	73.485	75.165	1.00	22.25
ATOM	169	CB	LEU	A	28	28.990	74.042	77.798	1.00	17.00
ATOM	170	CG	LEU	A	28	28.159	75.188	78.376	1.00	18.01
ATOM	171	CD1	LEU	A	28	26.847	75.547	77.733	1.00	14.28
ATOM	172	CD2	LEU	A	28	29.053	76.394	78.592	1.00	16.45
ATOM	173	N	ALA	A	29	29.478	72.767	75.193	1.00	23.87
ATOM	174	CA	ALA	A	29	29.598	72.827	73.707	1.00	22.62
ATOM	175	C	ALA	A	29	28.773	71.847	72.837	1.00	20.86
ATOM	176	O	ALA	A	29	28.192	72.239	71.830	1.00	25.89
ATOM	177	CB	ALA	A	29	31.065	72.692	73.326	1.00	20.24
ATOM	178	N	LEU	A	30	28.733	70.580	73.267	1.00	15.78
ATOM	179	CA	LEU	A	30	28.079	69.497	72.519	1.00	18.05
ATOM	180	C	LEU	A	30	26.557	69.416	72.559	1.00	22.38
ATOM	181	O	LEU	A	30	25.845	69.251	71.566	1.00	23.63
ATOM	182	CB	LEU	A	30	28.732	68.194	72.977	1.00	16.47
ATOM	183	CG	LEU	A	30	28.234	66.887	72.360	1.00	17.59
ATOM	184	CD1	LEU	A	30	28.812	65.706	73.120	1.00	12.95
ATOM	185	CD2	LEU	A	30	28.456	66.775	70.850	1.00	13.89
ATOM	186	N	LEU	A	31	26.075	69.533	73.812	1.00	22.39
ATOM	187	CA	LEU	A	31	24.633	69.430	74.049	1.00	18.84
ATOM	188	C	LEU	A	31	23.817	70.624	73.538	1.00	16.30
ATOM	189	O	LEU	A	31	24.260	71.763	73.576	1.00	19.93
ATOM	190	CB	LEU	A	31	24.381	69.199	75.556	1.00	16.94
ATOM	191	CG	LEU	A	31	24.923	67.873	76.095	1.00	17.95
ATOM	192	CD1	LEU	A	31	24.177	66.669	75.553	1.00	11.60
ATOM	193	CD2	LEU	A	31	24.823	67.878	77.628	1.00	18.77
ATOM	194	N	PRO	A	32	22.581	70.333	73.105	1.00	14.80
ATOM	195	CA	PRO	A	32	21.589	71.404	72.910	1.00	18.31
ATOM	196	C	PRO	A	32	21.228	72.028	74.278	1.00	22.24
ATOM	197	O	PRO	A	32	21.453	71.442	75.327	1.00	22.27
ATOM	198	CB	PRO	A	32	20.402	70.621	72.348	1.00	15.94
ATOM	199	CG	PRO	A	32	20.545	69.184	72.847	1.00	16.93
ATOM	200	CD	PRO	A	32	22.038	68.972	72.954	1.00	15.56
ATOM	201	N	PRO	A	33	20.657	73.249	74.287	1.00	23.41
ATOM	202	CA	PRO	A	33	20.190	73.780	75.586	1.00	20.34
ATOM	203	C	PRO	A	33	19.059	72.945	76.084	1.00	19.93
ATOM	204	O	PRO	A	33	18.409	72.292	75.285	1.00	18.67
ATOM	205	CB	PRO	A	33	19.659	75.158	75.224	1.00	18.52
ATOM	206	CG	PRO	A	33	20.267	75.499	73.877	1.00	21.71
ATOM	207	CD	PRO	A	33	20.406	74.146	73.177	1.00	21.12
ATOM	208	N	PRO	A	34	18.785	72.950	77.411	1.00	19.36
ATOM	209	CA	PRO	A	34	17.645	72.138	77.863	1.00	13.70
ATOM	210	C	PRO	A	34	16.348	72.759	77.351	1.00	11.77
ATOM	211	O	PRO	A	34	16.280	73.937	77.090	1.00	14.58
ATOM	212	CB	PRO	A	34	17.760	72.358	79.389	1.00	13.66
ATOM	213	CG	PRO	A	34	18.471	73.698	79.571	1.00	14.81
ATOM	214	CD	PRO	A	34	19.499	73.679	78.464	1.00	16.49
ATOM	215	N	PRO	A	35	15.257	72.007	77.284	1.00	12.52
ATOM	216	CA	PRO	A	35	14.011	72.710	76.973	1.00	13.71

FIG. 14

ATOM	217	C	PRO	A	35	13.665	73.842	77.945	1.00	20.26
ATOM	218	O	PRO	A	35	13.728	73.715	79.159	1.00	20.52
ATOM	219	CB	PRO	A	35	12.997	71.579	76.991	1.00	11.74
ATOM	220	CG	PRO	A	35	13.723	70.243	77.051	1.00	12.04
ATOM	221	CD	PRO	A	35	15.140	70.581	77.482	1.00	11.57
ATOM	222	N	ALA	A	36	13.311	74.962	77.356	1.00	19.25
ATOM	223	CA	ALA	A	36	12.919	76.136	78.122	1.00	18.78
ATOM	224	C	ALA	A	36	11.457	76.120	78.497	1.00	18.25
ATOM	225	O	ALA	A	36	10.582	75.579	77.847	1.00	18.88
ATOM	226	CB	ALA	A	36	13.152	77.414	77.304	1.00	17.95
ATOM	227	N	VAL	A	37	11.182	76.753	79.609	1.00	18.03
ATOM	228	CA	VAL	A	37	9.803	77.005	79.965	1.00	16.78
ATOM	229	C	VAL	A	37	9.135	77.993	78.998	1.00	17.18
ATOM	230	O	VAL	A	37	9.640	79.048	78.650	1.00	19.89
ATOM	231	CB	VAL	A	37	9.740	77.500	81.436	1.00	18.33
ATOM	232	CG1	VAL	A	37	10.381	76.501	82.418	1.00	13.83
ATOM	233	CG2	VAL	A	37	8.300	77.825	81.832	1.00	14.21
ATOM	234	N	GLY	A	38	7.952	77.616	78.561	1.00	18.34
ATOM	235	CA	GLY	A	38	7.422	78.249	77.343	1.00	22.06
ATOM	236	C	GLY	A	38	7.538	77.398	76.043	1.00	21.25
ATOM	237	O	GLY	A	38	6.851	77.623	75.068	1.00	22.09
ATOM	238	N	SER	A	39	8.422	76.401	76.060	1.00	21.73
ATOM	239	CA	SER	A	39	8.520	75.487	74.905	1.00	20.30
ATOM	240	C	SER	A	39	7.604	74.277	74.964	1.00	21.10
ATOM	241	O	SER	A	39	7.217	73.736	76.002	1.00	19.55
ATOM	242	CB	SER	A	39	9.946	74.998	74.748	1.00	15.45
ATOM	243	OG	SER	A	39	10.197	73.967	75.704	1.00	15.38
ATOM	244	N	ILE	A	40	7.287	73.796	73.772	1.00	17.17
ATOM	245	CA	ILE	A	40	6.618	72.485	73.702	1.00	14.71
ATOM	246	C	ILE	A	40	7.475	71.311	74.225	1.00	10.81
ATOM	247	O	ILE	A	40	6.998	70.315	74.782	1.00	15.23
ATOM	248	CB	ILE	A	40	6.102	72.235	72.219	1.00	15.78
ATOM	249	CG1	ILE	A	40	5.162	73.368	71.791	1.00	15.41
ATOM	250	CG2	ILE	A	40	5.406	70.863	72.091	1.00	14.54
ATOM	251	CD1	ILE	A	40	4.812	73.332	70.307	1.00	18.26
ATOM	252	N	ALA	A	41	8.790	71.443	74.040	1.00	10.69
ATOM	253	CA	ALA	A	41	9.633	70.373	74.530	1.00	13.79
ATOM	254	C	ALA	A	41	9.566	70.300	76.091	1.00	15.36
ATOM	255	O	ALA	A	41	9.369	69.245	76.683	1.00	20.02
ATOM	256	CB	ALA	A	41	11.046	70.610	74.065	1.00	11.61
ATOM	257	N	PHE	A	42	9.547	71.495	76.702	1.00	16.94
ATOM	258	CA	PHE	A	42	9.200	71.480	78.151	1.00	15.75
ATOM	259	C	PHE	A	42	7.818	70.970	78.533	1.00	16.07
ATOM	260	O	PHE	A	42	7.652	70.182	79.448	1.00	19.72
ATOM	261	CB	PHE	A	42	9.513	72.819	78.819	1.00	17.93
ATOM	262	CG	PHE	A	42	9.380	72.700	80.338	1.00	20.96
ATOM	263	CD1	PHE	A	42	10.297	71.904	81.056	1.00	19.46
ATOM	264	CD2	PHE	A	42	8.324	73.370	80.997	1.00	20.99
ATOM	265	CE1	PHE	A	42	10.148	71.763	82.450	1.00	17.30
ATOM	266	CE2	PHE	A	42	8.190	73.248	82.402	1.00	19.79
ATOM	267	CZ	PHE	A	42	9.111	72.443	83.100	1.00	13.36
ATOM	268	N	LEU	A	43	6.790	71.375	77.765	1.00	19.00
ATOM	269	CA	LEU	A	43	5.507	70.643	77.917	1.00	19.22
ATOM	270	C	LEU	A	43	5.573	69.103	77.945	1.00	19.39

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FIG. 15

ATOM	271	O	LEU	A	43	4.957	68.410	78.749	1.00	17.69
ATOM	272	CB	LEU	A	43	4.472	71.003	76.826	1.00	21.60
ATOM	273	CG	LEU	A	43	3.213	71.850	77.034	1.00	24.67
ATOM	274	CD1	LEU	A	43	2.597	71.800	78.433	1.00	17.68
ATOM	275	CD2	LEU	A	43	2.172	71.549	75.953	1.00	21.72
ATOM	276	N	ASN	A	44	6.392	68.588	77.023	1.00	19.47
ATOM	277	CA	ASN	A	44	6.653	67.176	77.076	1.00	19.82
ATOM	278	C	ASN	A	44	7.419	66.619	78.312	1.00	17.44
ATOM	279	O	ASN	A	44	7.018	65.604	78.855	1.00	15.52
ATOM	280	CB	ASN	A	44	7.259	66.847	75.747	1.00	19.07
ATOM	281	CG	ASN	A	44	7.491	65.366	75.643	1.00	22.97
ATOM	282	OD1	ASN	A	44	8.605	64.906	75.468	1.00	30.35
ATOM	283	ND2	ASN	A	44	6.444	64.588	75.862	1.00	22.13
ATOM	284	N	ASP	A	45	8.482	67.324	78.726	1.00	19.71
ATOM	285	CA	ASP	A	45	9.175	67.050	80.020	1.00	19.87
ATOM	286	C	ASP	A	45	8.192	66.977	81.213	1.00	19.30
ATOM	287	O	ASP	A	45	8.103	66.009	81.956	1.00	21.00
ATOM	288	CB	ASP	A	45	10.225	68.119	80.273	1.00	13.57
ATOM	289	CG	ASP	A	45	11.563	67.769	79.706	1.00	12.64
ATOM	290	OD1	ASP	A	45	12.408	68.656	79.625	1.00	15.68
ATOM	291	OD2	ASP	A	45	11.823	66.611	79.414	1.00	14.57
ATOM	292	N	GLN	A	46	7.347	68.007	81.299	1.00	19.62
ATOM	293	CA	GLN	A	46	6.199	67.904	82.220	1.00	19.44
ATOM	294	C	GLN	A	46	5.259	66.702	82.166	1.00	22.23
ATOM	295	O	GLN	A	46	4.960	66.057	83.175	1.00	21.67
ATOM	296	CB	GLN	A	46	5.353	69.153	82.218	1.00	16.35
ATOM	297	CG	GLN	A	46	6.282	70.333	82.395	1.00	18.35
ATOM	298	CD	GLN	A	46	5.398	71.519	82.591	1.00	26.07
ATOM	299	OE1	GLN	A	46	5.334	72.143	83.629	1.00	31.83
ATOM	300	NE2	GLN	A	46	4.622	71.823	81.591	1.00	22.82
ATOM	301	N	ALA	A	47	4.838	66.364	80.935	1.00	19.12
ATOM	302	CA	ALA	A	47	3.979	65.187	80.813	1.00	17.83
ATOM	303	C	ALA	A	47	4.661	63.871	81.172	1.00	15.90
ATOM	304	O	ALA	A	47	4.065	62.940	81.701	1.00	18.55
ATOM	305	CB	ALA	A	47	3.441	65.066	79.367	1.00	17.11
ATOM	306	N	MET	A	48	5.970	63.818	80.841	1.00	18.16
ATOM	307	CA	MET	A	48	6.799	62.644	81.235	1.00	19.52
ATOM	308	C	MET	A	48	7.012	62.460	82.765	1.00	21.38
ATOM	309	O	MET	A	48	6.996	61.358	83.316	1.00	20.83
ATOM	310	CB	MET	A	48	8.173	62.667	80.539	1.00	21.42
ATOM	311	CG	MET	A	48	8.150	62.603	78.984	1.00	29.81
ATOM	312	SD	MET	A	48	7.330	61.126	78.308	1.00	36.20
ATOM	313	CE	MET	A	48	5.582	61.633	78.280	1.00	33.60
ATOM	314	N	TYR	A	49	7.139	63.655	83.414	1.00	21.32
ATOM	315	CA	TYR	A	49	7.066	63.807	84.885	1.00	21.30
ATOM	316	C	TYR	A	49	5.773	63.244	85.515	1.00	22.58
ATOM	317	O	TYR	A	49	5.797	62.383	86.390	1.00	24.04
ATOM	318	CB	TYR	A	49	7.304	65.282	85.217	1.00	20.61
ATOM	319	CG	TYR	A	49	7.034	65.494	86.692	1.00	23.57
ATOM	320	CD1	TYR	A	49	5.755	65.931	87.109	1.00	23.57
ATOM	321	CD2	TYR	A	49	8.080	65.194	87.574	1.00	21.83
ATOM	322	CE1	TYR	A	49	5.524	66.097	88.481	1.00	26.09
ATOM	323	CE2	TYR	A	49	7.844	65.349	88.943	1.00	23.18
ATOM	324	CZ	TYR	A	49	6.591	65.842	89.377	1.00	26.31

FIG. 16

ATOM	325	OH	TYR	A	49	6.444	66.124	90.726	1.00	29.46
ATOM	326	N	GLU	A	50	4.639	63.731	84.994	1.00	22.09
ATOM	327	CA	GLU	A	50	3.336	63.234	85.472	1.00	21.48
ATOM	328	C	GLU	A	50	3.052	61.776	85.230	1.00	23.20
ATOM	329	O	GLU	A	50	2.548	61.050	86.081	1.00	24.23
ATOM	330	CB	GLU	A	50	2.190	64.023	84.862	1.00	21.88
ATOM	331	CG	GLU	A	50	2.304	65.537	84.986	1.00	21.13
ATOM	332	CD	GLU	A	50	2.054	65.976	86.417	1.00	25.41
ATOM	333	OE1	GLU	A	50	1.887	65.138	87.287	1.00	24.65
ATOM	334	OE2	GLU	A	50	2.004	67.162	86.679	1.00	25.05
ATOM	335	N	GLN	A	51	3.479	61.343	84.032	1.00	23.02
ATOM	336	CA	GLN	A	51	3.427	59.907	83.812	1.00	24.72
ATOM	337	C	GLN	A	51	4.275	59.006	84.728	1.00	26.23
ATOM	338	O	GLN	A	51	3.804	57.996	85.253	1.00	25.10
ATOM	339	CB	GLN	A	51	3.680	59.545	82.355	1.00	24.41
ATOM	340	CG	GLN	A	51	3.461	58.028	82.141	1.00	38.05
ATOM	341	CD	GLN	A	51	2.115	57.435	82.657	1.00	53.15
ATOM	342	OE1	GLN	A	51	1.093	58.076	82.867	1.00	61.03
ATOM	343	NE2	GLN	A	51	2.098	56.123	82.834	1.00	55.24
ATOM	344	N	GLY	A	52	5.556	59.414	84.922	1.00	26.76
ATOM	345	CA	GLY	A	52	6.400	58.689	85.876	1.00	26.91
ATOM	346	C	GLY	A	52	5.793	58.681	87.286	1.00	25.60
ATOM	347	O	GLY	A	52	5.666	57.699	87.997	1.00	24.37
ATOM	348	N	ARG	A	53	5.321	59.874	87.621	1.00	28.09
ATOM	349	CA	ARG	A	53	4.527	60.032	88.834	1.00	29.75
ATOM	350	C	ARG	A	53	3.384	59.049	89.067	1.00	32.01
ATOM	351	O	ARG	A	53	3.284	58.437	90.115	1.00	34.69
ATOM	352	CB	ARG	A	53	4.128	61.494	88.965	1.00	30.41
ATOM	353	CG	ARG	A	53	3.857	61.919	90.389	1.00	29.15
ATOM	354	CD	ARG	A	53	3.519	63.393	90.461	1.00	29.38
ATOM	355	NE	ARG	A	53	2.385	63.740	89.609	1.00	31.35
ATOM	356	CZ	ARG	A	53	1.088	63.593	89.886	1.00	32.29
ATOM	357	NH1	ARG	A	53	0.187	64.144	89.125	1.00	32.06
ATOM	358	NH2	ARG	A	53	0.661	62.938	90.931	1.00	32.66
ATOM	359	N	LEU	A	54	2.575	58.839	88.033	1.00	32.47
ATOM	360	CA	LEU	A	54	1.588	57.735	88.076	1.00	31.67
ATOM	361	C	LEU	A	54	2.114	56.273	88.119	1.00	33.30
ATOM	362	O	LEU	A	54	1.452	55.329	88.568	1.00	35.90
ATOM	363	CB	LEU	A	54	0.603	57.880	86.901	1.00	33.52
ATOM	364	CG	LEU	A	54	-0.599	58.822	87.055	1.00	32.85
ATOM	365	CD1	LEU	A	54	-1.298	59.020	85.709	1.00	30.53
ATOM	366	CD2	LEU	A	54	-0.286	60.130	87.777	1.00	36.56
ATOM	367	N	LEU	A	55	3.374	56.117	87.657	1.00	31.95
ATOM	368	CA	LEU	A	55	4.016	54.784	87.735	1.00	32.70
ATOM	369	C	LEU	A	55	4.577	54.392	89.091	1.00	33.98
ATOM	370	O	LEU	A	55	4.842	53.224	89.386	1.00	32.73
ATOM	371	CB	LEU	A	55	5.194	54.646	86.790	1.00	31.04
ATOM	372	CG	LEU	A	55	4.832	54.514	85.343	1.00	28.60
ATOM	373	CD1	LEU	A	55	3.960	53.287	85.101	1.00	27.88
ATOM	374	CD2	LEU	A	55	6.118	54.471	84.539	1.00	28.33
ATOM	375	N	ARG	A	56	4.732	55.458	89.911	1.00	36.20
ATOM	376	CA	ARG	A	56	5.257	55.308	91.281	1.00	37.04
ATOM	377	C	ARG	A	56	4.616	54.240	92.164	1.00	40.28
ATOM	378	O	ARG	A	56	5.260	53.518	92.907	1.00	41.22

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FIG. 17

ATOM	379	CB	ARG	A	56	5.249	56.643	91.993	1.00	32.58
ATOM	380	CG	ARG	A	56	6.368	57.502	91.476	1.00	22.04
ATOM	381	CD	ARG	A	56	6.142	58.874	92.049	1.00	21.74
ATOM	382	NE	ARG	A	56	7.073	59.804	91.447	1.00	23.56
ATOM	383	CZ	ARG	A	56	7.062	61.074	91.750	1.00	25.56
ATOM	384	NH1	ARG	A	56	6.401	61.444	92.790	1.00	30.94
ATOM	385	NH2	ARG	A	56	7.688	61.979	91.035	1.00	22.33
ATOM	386	N	ASN	A	57	3.306	54.120	91.997	1.00	44.42
ATOM	387	CA	ASN	A	57	2.602	53.027	92.680	1.00	48.62
ATOM	388	C	ASN	A	57	2.786	51.585	92.169	1.00	47.46
ATOM	389	O	ASN	A	57	2.316	50.630	92.759	1.00	51.15
ATOM	390	CB	ASN	A	57	1.124	53.435	92.726	1.00	59.30
ATOM	391	CG	ASN	A	57	0.389	53.137	94.049	1.00	68.98
ATOM	392	OD1	ASN	A	57	-0.829	53.335	94.164	1.00	75.09
ATOM	393	ND2	ASN	A	57	1.140	52.692	95.058	1.00	71.68
ATOM	394	N	THR	A	58	3.461	51.442	91.036	1.00	42.68
ATOM	395	CA	THR	A	58	3.555	50.086	90.475	1.00	36.64
ATOM	396	C	THR	A	58	4.821	49.318	90.871	1.00	33.64
ATOM	397	O	THR	A	58	5.721	49.876	91.477	1.00	31.69
ATOM	398	CB	THR	A	58	3.492	50.189	88.948	1.00	36.81
ATOM	399	OG1	THR	A	58	4.774	50.576	88.447	1.00	37.64
ATOM	400	CG2	THR	A	58	2.432	51.203	88.507	1.00	35.36
ATOM	401	N	GLU	A	59	4.937	48.068	90.409	1.00	33.08
ATOM	402	CA	GLU	A	59	6.238	47.410	90.581	1.00	34.80
ATOM	403	C	GLU	A	59	7.487	48.104	89.944	1.00	33.45
ATOM	404	O	GLU	A	59	8.607	48.153	90.463	1.00	34.28
ATOM	405	CB	GLU	A	59	6.067	45.933	90.191	1.00	43.43
ATOM	406	CG	GLU	A	59	7.242	45.007	90.614	1.00	59.74
ATOM	407	CD	GLU	A	59	7.519	44.933	92.159	1.00	69.61
ATOM	408	OE1	GLU	A	59	6.582	45.064	92.960	1.00	74.78
ATOM	409	OE2	GLU	A	59	8.686	44.751	92.589	1.00	74.97
ATOM	410	N	ARG	A	60	7.229	48.734	88.768	1.00	27.61
ATOM	411	CA	ARG	A	60	8.251	49.599	88.158	1.00	25.02
ATOM	412	C	ARG	A	60	8.614	50.851	88.958	1.00	22.94
ATOM	413	O	ARG	A	60	9.772	51.257	89.002	1.00	24.63
ATOM	414	CB	ARG	A	60	7.874	49.966	86.690	1.00	26.16
ATOM	415	CG	ARG	A	60	8.877	50.860	85.900	1.00	24.47
ATOM	416	CD	ARG	A	60	10.268	50.249	85.758	1.00	23.96
ATOM	417	NE	ARG	A	60	11.285	51.161	85.217	1.00	25.64
ATOM	418	CZ	ARG	A	60	12.214	51.778	85.945	1.00	24.77
ATOM	419	NH1	ARG	A	60	12.159	51.805	87.261	1.00	24.78
ATOM	420	NH2	ARG	A	60	13.227	52.294	85.325	1.00	19.79
ATOM	421	N	GLY	A	61	7.562	51.411	89.587	1.00	21.94
ATOM	422	CA	GLY	A	61	7.623	52.443	90.620	1.00	22.33
ATOM	423	C	GLY	A	61	8.468	52.051	91.824	1.00	24.44
ATOM	424	O	GLY	A	61	9.350	52.773	92.253	1.00	25.22
ATOM	425	N	LYS	A	62	8.248	50.821	92.307	1.00	26.95
ATOM	426	CA	LYS	A	62	9.102	50.251	93.350	1.00	26.24
ATOM	427	C	LYS	A	62	10.590	50.158	93.045	1.00	24.89
ATOM	428	O	LYS	A	62	11.443	50.668	93.756	1.00	23.23
ATOM	429	CB	LYS	A	62	8.519	48.900	93.723	1.00	29.90
ATOM	430	CG	LYS	A	62	9.379	48.296	94.835	1.00	38.76
ATOM	431	CD	LYS	A	62	8.847	46.904	95.222	1.00	47.47
ATOM	432	CE	LYS	A	62	9.944	45.971	95.773	1.00	53.72

FIG. 18

ATOM	433	NZ	LYS	A	62	10.167	44.857	94.832	1.00	60.22
ATOM	434	N	LEU	A	63	10.866	49.560	91.882	1.00	24.67
ATOM	435	CA	LEU	A	63	12.239	49.634	91.346	1.00	23.65
ATOM	436	C	LEU	A	63	12.805	51.043	91.186	1.00	22.74
ATOM	437	O	LEU	A	63	13.927	51.359	91.517	1.00	25.19
ATOM	438	CB	LEU	A	63	12.232	48.973	89.981	1.00	27.11
ATOM	439	CG	LEU	A	63	13.477	48.298	89.403	1.00	31.83
ATOM	440	CD1	LEU	A	63	14.808	48.658	90.077	1.00	33.84
ATOM	441	CD2	LEU	A	63	13.440	48.410	87.874	1.00	26.95
ATOM	442	N	ALA	A	64	11.979	51.940	90.642	1.00	21.62
ATOM	443	CA	ALA	A	64	12.492	53.308	90.539	1.00	20.51
ATOM	444	C	ALA	A	64	12.862	53.971	91.863	1.00	21.79
ATOM	445	O	ALA	A	64	13.890	54.636	91.984	1.00	21.21
ATOM	446	CB	ALA	A	64	11.456	54.196	89.862	1.00	19.01
ATOM	447	N	ALA	A	65	11.984	53.747	92.870	1.00	23.25
ATOM	448	CA	ALA	A	65	12.374	54.212	94.235	1.00	24.88
ATOM	449	C	ALA	A	65	13.684	53.619	94.784	1.00	22.62
ATOM	450	O	ALA	A	65	14.551	54.328	95.268	1.00	22.95
ATOM	451	CB	ALA	A	65	11.249	54.013	95.265	1.00	25.38
ATOM	452	N	GLU	A	66	13.848	52.295	94.572	1.00	23.38
ATOM	453	CA	GLU	A	66	15.116	51.632	94.878	1.00	23.41
ATOM	454	C	GLU	A	66	16.332	52.188	94.152	1.00	26.06
ATOM	455	O	GLU	A	66	17.321	52.604	94.744	1.00	25.12
ATOM	456	CB	GLU	A	66	14.968	50.136	94.665	1.00	25.85
ATOM	457	CG	GLU	A	66	13.818	49.616	95.533	1.00	31.94
ATOM	458	CD	GLU	A	66	13.546	48.142	95.293	1.00	37.59
ATOM	459	OE1	GLU	A	66	13.147	47.430	96.220	1.00	40.33
ATOM	460	OE2	GLU	A	66	13.721	47.673	94.176	1.00	40.79
ATOM	461	N	ASP	A	67	16.204	52.276	92.817	1.00	24.01
ATOM	462	CA	ASP	A	67	17.222	52.928	91.986	1.00	19.72
ATOM	463	C	ASP	A	67	17.549	54.333	92.402	1.00	16.72
ATOM	464	O	ASP	A	67	18.694	54.767	92.414	1.00	18.91
ATOM	465	CB	ASP	A	67	16.787	52.944	90.495	1.00	21.68
ATOM	466	CG	ASP	A	67	16.824	51.580	89.801	1.00	25.22
ATOM	467	OD1	ASP	A	67	17.340	50.629	90.370	1.00	23.32
ATOM	468	OD2	ASP	A	67	16.349	51.434	88.666	1.00	26.83
ATOM	469	N	ALA	A	68	16.485	55.059	92.773	1.00	16.48
ATOM	470	CA	ALA	A	68	16.685	56.425	93.250	1.00	19.28
ATOM	471	C	ALA	A	68	17.489	56.510	94.569	1.00	20.86
ATOM	472	O	ALA	A	68	18.165	57.494	94.837	1.00	22.07
ATOM	473	CB	ALA	A	68	15.330	57.134	93.419	1.00	19.81
ATOM	474	N	ASN	A	69	17.472	55.371	95.299	1.00	23.11
ATOM	475	CA	ASN	A	69	18.330	55.262	96.514	1.00	27.41
ATOM	476	C	ASN	A	69	19.816	55.042	96.273	1.00	29.49
ATOM	477	O	ASN	A	69	20.646	55.304	97.140	1.00	28.64
ATOM	478	CB	ASN	A	69	17.933	54.145	97.466	1.00	24.19
ATOM	479	CG	ASN	A	69	16.632	54.425	98.142	1.00	25.79
ATOM	480	OD1	ASN	A	69	16.298	55.549	98.445	1.00	26.84
ATOM	481	ND2	ASN	A	69	15.894	53.359	98.410	1.00	30.16
ATOM	482	N	LEU	A	70	20.104	54.574	95.034	1.00	25.30
ATOM	483	CA	LEU	A	70	21.514	54.442	94.627	1.00	23.20
ATOM	484	C	LEU	A	70	22.329	55.691	94.640	1.00	21.41
ATOM	485	O	LEU	A	70	22.013	56.696	94.028	1.00	23.50
ATOM	486	CB	LEU	A	70	21.672	53.890	93.225	1.00	22.19

FIG. 19

ATOM	487	CG	LEU	A	70	21.078	52.512	93.095	1.00	22.16
ATOM	488	CD1	LEU	A	70	21.830	51.459	93.896	1.00	20.70
ATOM	489	CD2	LEU	A	70	21.016	52.154	91.624	1.00	23.47
ATOM	490	N	SER	A	71	23.450	55.563	95.304	1.00	21.73
ATOM	491	CA	SER	A	71	24.527	56.515	95.119	1.00	22.25
ATOM	492	C	SER	A	71	25.355	56.171	93.888	1.00	20.52
ATOM	493	O	SER	A	71	25.269	55.081	93.357	1.00	23.70
ATOM	494	CB	SER	A	71	25.453	56.521	96.349	1.00	22.74
ATOM	495	OG	SER	A	71	26.232	55.303	96.432	1.00	28.68
ATOM	496	N	SER	A	72	26.220	57.079	93.445	1.00	20.02
ATOM	497	CA	SER	A	72	27.096	56.747	92.294	1.00	20.88
ATOM	498	C	SER	A	72	27.860	55.479	92.410	1.00	22.52
ATOM	499	O	SER	A	72	27.979	54.663	91.518	1.00	21.65
ATOM	500	CB	SER	A	72	28.113	57.834	92.083	1.00	19.05
ATOM	501	OG	SER	A	72	27.352	58.966	91.735	1.00	22.00
ATOM	502	N	GLY	A	73	28.336	55.318	93.640	1.00	20.71
ATOM	503	CA	GLY	A	73	28.979	54.068	94.006	1.00	16.81
ATOM	504	C	GLY	A	73	28.146	52.783	93.939	1.00	15.97
ATOM	505	O	GLY	A	73	28.697	51.705	93.753	1.00	20.02
ATOM	506	N	GLY	A	74	26.818	52.915	94.046	1.00	16.07
ATOM	507	CA	GLY	A	74	26.090	51.649	93.967	1.00	18.17
ATOM	508	C	GLY	A	74	25.671	51.260	92.526	1.00	21.98
ATOM	509	O	GLY	A	74	25.202	50.164	92.238	1.00	21.28
ATOM	510	N	VAL	A	75	25.887	52.210	91.567	1.00	22.48
ATOM	511	CA	VAL	A	75	25.521	51.777	90.174	1.00	22.71
ATOM	512	C	VAL	A	75	26.174	50.493	89.628	1.00	18.50
ATOM	513	O	VAL	A	75	25.497	49.573	89.210	1.00	20.32
ATOM	514	CB	VAL	A	75	25.820	52.946	89.218	1.00	23.52
ATOM	515	CG1	VAL	A	75	25.719	52.707	87.712	1.00	21.49
ATOM	516	CG2	VAL	A	75	25.153	54.265	89.560	1.00	17.54
ATOM	517	N	ALA	A	76	27.517	50.394	89.738	1.00	21.05
ATOM	518	CA	ALA	A	76	28.149	49.125	89.372	1.00	20.51
ATOM	519	C	ALA	A	76	27.414	47.875	89.826	1.00	24.64
ATOM	520	O	ALA	A	76	27.033	47.028	89.015	1.00	24.90
ATOM	521	CB	ALA	A	76	29.612	49.071	89.810	1.00	19.14
ATOM	522	N	ASN	A	77	27.131	47.820	91.145	1.00	20.97
ATOM	523	CA	ASN	A	77	26.463	46.601	91.622	1.00	17.62
ATOM	524	C	ASN	A	77	25.019	46.464	91.205	1.00	16.57
ATOM	525	O	ASN	A	77	24.536	45.350	91.024	1.00	19.24
ATOM	526	CB	ASN	A	77	26.615	46.509	93.137	1.00	23.52
ATOM	527	CG	ASN	A	77	25.817	45.362	93.677	1.00	21.57
ATOM	528	OD1	ASN	A	77	24.672	45.508	94.079	1.00	26.66
ATOM	529	ND2	ASN	A	77	26.435	44.202	93.627	1.00	24.64
ATOM	530	N	ALA	A	78	24.377	47.638	91.017	1.00	17.23
ATOM	531	CA	ALA	A	78	23.060	47.710	90.339	1.00	18.62
ATOM	532	C	ALA	A	78	22.874	47.025	88.941	1.00	19.92
ATOM	533	O	ALA	A	78	21.767	46.705	88.517	1.00	21.04
ATOM	534	CB	ALA	A	78	22.636	49.160	90.208	1.00	13.62
ATOM	535	N	PHE	A	79	24.025	46.748	88.292	1.00	19.22
ATOM	536	CA	PHE	A	79	24.019	45.921	87.070	1.00	20.71
ATOM	537	C	PHE	A	79	24.117	44.420	87.238	1.00	23.30
ATOM	538	O	PHE	A	79	24.161	43.662	86.273	1.00	23.64
ATOM	539	CB	PHE	A	79	25.116	46.352	86.082	1.00	18.00
ATOM	540	CG	PHE	A	79	24.821	47.683	85.382	1.00	19.59

FIG. 20

ATOM	541	CD1	PHE	A	79	25.181	48.903	85.984	1.00	17.05
ATOM	542	CD2	PHE	A	79	24.214	47.687	84.104	1.00	18.56
ATOM	543	CE1	PHE	A	79	25.026	50.119	85.298	1.00	19.06
ATOM	544	CE2	PHE	A	79	24.040	48.906	83.419	1.00	15.97
ATOM	545	CZ	PHE	A	79	24.500	50.104	83.989	1.00	17.87
ATOM	546	N	SER	A	80	24.150	43.947	88.488	1.00	19.74
ATOM	547	CA	SER	A	80	24.500	42.511	88.632	1.00	17.29
ATOM	548	C	SER	A	80	23.601	41.501	87.944	1.00	18.57
ATOM	549	O	SER	A	80	23.977	40.494	87.339	1.00	22.38
ATOM	550	CB	SER	A	80	24.608	42.106	90.125	1.00	15.17
ATOM	551	OG	SER	A	80	25.646	42.920	90.700	1.00	17.32
ATOM	552	N	GLY	A	81	22.309	41.852	88.041	1.00	19.68
ATOM	553	CA	GLY	A	81	21.271	41.005	87.413	1.00	22.50
ATOM	554	C	GLY	A	81	21.293	40.977	85.855	1.00	24.85
ATOM	555	O	GLY	A	81	21.318	39.939	85.211	1.00	23.46
ATOM	556	N	ALA	A	82	21.380	42.197	85.279	1.00	24.60
ATOM	557	CA	ALA	A	82	21.686	42.339	83.855	1.00	24.50
ATOM	558	C	ALA	A	82	22.985	41.643	83.417	1.00	25.22
ATOM	559	O	ALA	A	82	23.000	40.873	82.468	1.00	23.42
ATOM	560	CB	ALA	A	82	21.649	43.819	83.470	1.00	20.35
ATOM	561	N	PHE	A	83	24.050	41.874	84.197	1.00	23.76
ATOM	562	CA	PHE	A	83	25.319	41.242	83.894	1.00	21.76
ATOM	563	C	PHE	A	83	25.325	39.726	83.974	1.00	22.85
ATOM	564	O	PHE	A	83	26.090	39.052	83.322	1.00	25.72
ATOM	565	CB	PHE	A	83	26.349	41.867	84.792	1.00	20.01
ATOM	566	CG	PHE	A	83	27.770	41.527	84.394	1.00	20.95
ATOM	567	CD1	PHE	A	83	28.486	40.587	85.152	1.00	16.94
ATOM	568	CD2	PHE	A	83	28.391	42.208	83.307	1.00	23.09
ATOM	569	CE1	PHE	A	83	29.841	40.355	84.843	1.00	18.79
ATOM	570	CE2	PHE	A	83	29.751	41.991	83.001	1.00	20.95
ATOM	571	CZ	PHE	A	83	30.474	41.069	83.795	1.00	21.43
ATOM	572	N	GLY	A	84	24.409	39.187	84.768	1.00	22.31
ATOM	573	CA	GLY	A	84	24.478	37.740	84.865	1.00	24.39
ATOM	574	C	GLY	A	84	25.199	37.163	86.093	1.00	29.49
ATOM	575	O	GLY	A	84	25.158	35.963	86.362	1.00	32.27
ATOM	576	N	SER	A	85	25.873	38.058	86.843	1.00	30.33
ATOM	577	CA	SER	A	85	26.685	37.625	88.001	1.00	28.46
ATOM	578	C	SER	A	85	27.047	38.788	88.936	1.00	29.06
ATOM	579	O	SER	A	85	26.915	39.945	88.556	1.00	29.00
ATOM	580	CB	SER	A	85	27.915	36.861	87.536	1.00	24.04
ATOM	581	OG	SER	A	85	28.903	37.746	87.028	1.00	28.11
ATOM	582	N	PRO	A	86	27.436	38.518	90.216	1.00	29.45
ATOM	583	CA	PRO	A	86	27.599	39.650	91.122	1.00	26.27
ATOM	584	C	PRO	A	86	28.721	40.513	90.733	1.00	22.75
ATOM	585	O	PRO	A	86	29.830	40.064	90.530	1.00	22.43
ATOM	586	CB	PRO	A	86	27.873	39.029	92.493	1.00	27.52
ATOM	587	CG	PRO	A	86	27.284	37.627	92.399	1.00	27.61
ATOM	588	CD	PRO	A	86	27.591	37.258	90.945	1.00	31.08
ATOM	589	N	ILE	A	87	28.350	41.776	90.659	1.00	22.99
ATOM	590	CA	ILE	A	87	29.363	42.816	90.469	1.00	24.80
ATOM	591	C	ILE	A	87	29.642	43.494	91.811	1.00	25.76
ATOM	592	O	ILE	A	87	28.956	44.424	92.220	1.00	24.68
ATOM	593	CB	ILE	A	87	28.908	43.860	89.427	1.00	24.26
ATOM	594	CG1	ILE	A	87	28.626	43.165	88.076	1.00	23.29

FIG. 21

ATOM	595	CG2	ILE	A	87	29.997	44.923	89.306	1.00	23.62
ATOM	596	CD1	ILE	A	87	27.925	44.100	87.092	1.00	21.95
ATOM	597	N	THR	A	88	30.655	42.914	92.481	1.00	25.86
ATOM	598	CA	THR	A	88	30.925	43.247	93.903	1.00	25.48
ATOM	599	C	THR	A	88	32.418	43.249	94.166	1.00	25.25
ATOM	600	O	THR	A	88	33.131	42.561	93.445	1.00	24.26
ATOM	601	CB	THR	A	88	30.332	42.211	94.859	1.00	22.31
ATOM	602	OG1	THR	A	88	31.102	41.029	94.702	1.00	25.42
ATOM	603	CG2	THR	A	88	28.833	41.943	94.710	1.00	19.45
ATOM	604	N	GLU	A	89	32.891	43.970	95.204	1.00	26.63
ATOM	605	CA	GLU	A	89	34.322	43.845	95.577	1.00	25.29
ATOM	606	C	GLU	A	89	34.810	42.429	95.889	1.00	25.30
ATOM	607	O	GLU	A	89	35.924	41.999	95.611	1.00	26.30
ATOM	608	CB	GLU	A	89	34.652	44.773	96.741	1.00	25.64
ATOM	609	CG	GLU	A	89	34.334	46.193	96.340	1.00	26.52
ATOM	610	CD	GLU	A	89	34.551	47.228	97.414	1.00	29.70
ATOM	611	OE1	GLU	A	89	35.136	48.245	97.123	1.00	33.05
ATOM	612	OE2	GLU	A	89	34.138	47.077	98.540	1.00	27.59
ATOM	613	N	LYS	A	90	33.860	41.697	96.459	1.00	26.25
ATOM	614	CA	LYS	A	90	34.095	40.310	96.883	1.00	28.81
ATOM	615	C	LYS	A	90	34.285	39.313	95.780	1.00	28.19
ATOM	616	O	LYS	A	90	35.206	38.518	95.773	1.00	30.49
ATOM	617	CB	LYS	A	90	32.889	39.869	97.672	1.00	31.00
ATOM	618	CG	LYS	A	90	32.956	38.478	98.228	1.00	37.00
ATOM	619	CD	LYS	A	90	31.536	38.026	98.583	1.00	43.53
ATOM	620	CE	LYS	A	90	31.386	36.504	98.712	1.00	50.17
ATOM	621	NZ	LYS	A	90	32.257	35.875	97.701	1.00	60.80
ATOM	622	N	ASP	A	91	33.324	39.416	94.870	1.00	28.68
ATOM	623	CA	ASP	A	91	33.271	38.504	93.738	1.00	29.34
ATOM	624	C	ASP	A	91	33.911	38.947	92.420	1.00	29.37
ATOM	625	O	ASP	A	91	34.429	38.173	91.635	1.00	31.54
ATOM	626	CB	ASP	A	91	31.827	38.162	93.438	1.00	30.91
ATOM	627	CG	ASP	A	91	31.087	37.722	94.674	1.00	31.69
ATOM	628	OD1	ASP	A	91	31.395	36.657	95.212	1.00	35.66
ATOM	629	OD2	ASP	A	91	30.186	38.438	95.088	1.00	29.63
ATOM	630	N	ALA	A	92	33.830	40.240	92.165	1.00	28.62
ATOM	631	CA	ALA	A	92	34.443	40.713	90.919	1.00	26.75
ATOM	632	C	ALA	A	92	35.255	41.981	91.131	1.00	26.94
ATOM	633	O	ALA	A	92	34.937	43.081	90.690	1.00	26.94
ATOM	634	CB	ALA	A	92	33.390	40.934	89.817	1.00	23.93
ATOM	635	N	PRO	A	93	36.336	41.826	91.930	1.00	27.16
ATOM	636	CA	PRO	A	93	37.151	43.015	92.274	1.00	25.78
ATOM	637	C	PRO	A	93	37.832	43.865	91.160	1.00	24.62
ATOM	638	O	PRO	A	93	37.844	45.098	91.178	1.00	22.75
ATOM	639	CB	PRO	A	93	38.120	42.411	93.292	1.00	25.31
ATOM	640	CG	PRO	A	93	38.219	40.926	92.945	1.00	23.54
ATOM	641	CD	PRO	A	93	36.817	40.578	92.534	1.00	25.29
ATOM	642	N	ALA	A	94	38.409	43.174	90.170	1.00	25.16
ATOM	643	CA	ALA	A	94	38.954	43.886	89.005	1.00	23.77
ATOM	644	C	ALA	A	94	37.923	44.715	88.249	1.00	17.72
ATOM	645	O	ALA	A	94	38.116	45.897	88.005	1.00	19.91
ATOM	646	CB	ALA	A	94	39.676	42.931	88.058	1.00	21.52
ATOM	647	N	LEU	A	95	36.787	44.081	88.026	1.00	19.68
ATOM	648	CA	LEU	A	95	35.577	44.770	87.539	1.00	20.23

FIG. 22

ATOM	649	C	LEU	A	95	35.001	45.902	88.385	1.00	21.85
ATOM	650	O	LEU	A	95	34.809	47.026	87.943	1.00	21.66
ATOM	651	CB	LEU	A	95	34.466	43.755	87.271	1.00	20.70
ATOM	652	CG	LEU	A	95	33.250	44.285	86.467	1.00	21.32
ATOM	653	CD1	LEU	A	95	32.299	43.149	86.063	1.00	20.10
ATOM	654	CD2	LEU	A	95	33.698	45.111	85.240	1.00	20.93
ATOM	655	N	HIS	A	96	34.755	45.606	89.667	1.00	21.70
ATOM	656	CA	HIS	A	96	34.313	46.691	90.543	1.00	17.84
ATOM	657	C	HIS	A	96	35.214	47.924	90.580	1.00	17.76
ATOM	658	O	HIS	A	96	34.767	49.069	90.496	1.00	19.44
ATOM	659	CB	HIS	A	96	34.042	46.116	91.937	1.00	20.62
ATOM	660	CG	HIS	A	96	32.934	46.893	92.613	1.00	21.96
ATOM	661	ND1	HIS	A	96	33.021	48.094	93.229	1.00	21.34
ATOM	662	CD2	HIS	A	96	31.614	46.470	92.680	1.00	24.62
ATOM	663	CE1	HIS	A	96	31.790	48.442	93.690	1.00	18.16
ATOM	664	NE2	HIS	A	96	30.923	47.437	93.338	1.00	23.59
ATOM	665	N	LYS	A	97	36.539	47.639	90.629	1.00	18.11
ATOM	666	CA	LYS	A	97	37.544	48.713	90.581	1.00	18.50
ATOM	667	C	LYS	A	97	37.519	49.564	89.317	1.00	20.80
ATOM	668	O	LYS	A	97	37.452	50.781	89.373	1.00	21.08
ATOM	669	CB	LYS	A	97	38.924	48.085	90.766	1.00	17.26
ATOM	670	CG	LYS	A	97	40.125	49.014	90.594	1.00	21.24
ATOM	671	CD	LYS	A	97	40.283	50.213	91.525	1.00	30.10
ATOM	672	CE	LYS	A	97	41.482	51.160	91.164	1.00	33.55
ATOM	673	NZ	LYS	A	97	41.557	52.449	91.915	1.00	29.55
ATOM	674	N	LEU	A	98	37.532	48.857	88.155	1.00	22.36
ATOM	675	CA	LEU	A	98	37.291	49.555	86.851	1.00	22.04
ATOM	676	C	LEU	A	98	36.128	50.581	86.806	1.00	17.59
ATOM	677	O	LEU	A	98	36.223	51.763	86.522	1.00	18.13
ATOM	678	CB	LEU	A	98	37.025	48.477	85.780	1.00	21.44
ATOM	679	CG	LEU	A	98	36.766	49.042	84.375	1.00	20.93
ATOM	680	CD1	LEU	A	98	36.265	47.902	83.493	1.00	22.92
ATOM	681	CD2	LEU	A	98	37.963	49.801	83.811	1.00	18.27
ATOM	682	N	LEU	A	99	34.977	50.024	87.188	1.00	19.16
ATOM	683	CA	LEU	A	99	33.753	50.802	87.186	1.00	18.37
ATOM	684	C	LEU	A	99	33.644	51.930	88.169	1.00	20.61
ATOM	685	O	LEU	A	99	33.068	52.964	87.883	1.00	18.31
ATOM	686	CB	LEU	A	99	32.545	49.874	87.263	1.00	18.90
ATOM	687	CG	LEU	A	99	32.428	48.860	86.191	1.00	20.87
ATOM	688	CD1	LEU	A	99	32.464	49.503	84.841	1.00	14.73
ATOM	689	CD2	LEU	A	99	31.190	48.099	86.497	1.00	19.82
ATOM	690	N	THR	A	100	34.252	51.692	89.359	1.00	22.03
ATOM	691	CA	THR	A	100	34.357	52.777	90.360	1.00	19.41
ATOM	692	C	THR	A	100	35.259	53.938	89.957	1.00	16.72
ATOM	693	O	THR	A	100	34.984	55.118	90.136	1.00	16.55
ATOM	694	CB	THR	A	100	34.889	52.174	91.674	1.00	19.50
ATOM	695	OG1	THR	A	100	34.030	51.113	92.091	1.00	19.99
ATOM	696	CG2	THR	A	100	35.092	53.221	92.758	1.00	21.12
ATOM	697	N	ASN	A	101	36.397	53.537	89.358	1.00	20.56
ATOM	698	CA	ASN	A	101	37.415	54.515	88.998	1.00	19.91
ATOM	699	C	ASN	A	101	37.022	55.479	87.873	1.00	21.88
ATOM	700	O	ASN	A	101	37.610	56.546	87.711	1.00	22.38
ATOM	701	CB	ASN	A	101	38.692	53.763	88.716	1.00	20.98
ATOM	702	CG	ASN	A	101	39.950	54.556	89.041	1.00	22.36

FIG. 23

ATOM	703	OD1	ASN	A	101	40.938	53.978	89.459	1.00	30.43
ATOM	704	ND2	ASN	A	101	39.964	55.868	88.889	1.00	23.45
ATOM	705	N	MET	A	102	35.952	55.090	87.154	1.00	21.94
ATOM	706	CA	MET	A	102	35.407	55.984	86.103	1.00	22.28
ATOM	707	C	MET	A	102	34.142	56.755	86.455	1.00	22.36
ATOM	708	O	MET	A	102	33.571	57.482	85.638	1.00	23.37
ATOM	709	CB	MET	A	102	35.162	55.213	84.781	1.00	19.03
ATOM	710	CG	MET	A	102	34.239	54.001	84.972	1.00	18.05
ATOM	711	SD	MET	A	102	33.744	53.082	83.481	1.00	20.07
ATOM	712	CE	MET	A	102	32.429	54.165	83.010	1.00	16.04
ATOM	713	N	ILE	A	103	33.681	56.555	87.724	1.00	21.00
ATOM	714	CA	ILE	A	103	32.441	57.221	88.180	1.00	18.78
ATOM	715	C	ILE	A	103	32.371	58.697	87.833	1.00	17.38
ATOM	716	O	ILE	A	103	31.413	59.152	87.245	1.00	18.08
ATOM	717	CB	ILE	A	103	32.174	57.025	89.732	1.00	16.18
ATOM	718	CG1	ILE	A	103	31.696	55.603	90.031	1.00	19.21
ATOM	719	CG2	ILE	A	103	31.135	58.037	90.272	1.00	12.63
ATOM	720	CD1	ILE	A	103	31.708	55.185	91.522	1.00	17.58
ATOM	721	N	GLU	A	104	33.426	59.429	88.218	1.00	18.81
ATOM	722	CA	GLU	A	104	33.369	60.900	88.092	1.00	18.36
ATOM	723	C	GLU	A	104	33.828	61.520	86.772	1.00	19.60
ATOM	724	O	GLU	A	104	33.420	62.606	86.365	1.00	19.13
ATOM	725	CB	GLU	A	104	34.092	61.600	89.241	1.00	18.56
ATOM	726	CG	GLU	A	104	33.446	61.448	90.617	1.00	19.21
ATOM	727	CD	GLU	A	104	31.994	61.944	90.665	1.00	23.36
ATOM	728	OE1	GLU	A	104	31.225	61.359	91.382	1.00	26.94
ATOM	729	OE2	GLU	A	104	31.574	62.888	90.013	1.00	28.46
ATOM	730	N	ASP	A	105	34.606	60.713	86.049	1.00	18.95
ATOM	731	CA	ASP	A	105	34.743	60.936	84.587	1.00	17.40
ATOM	732	C	ASP	A	105	33.378	61.099	83.886	1.00	15.12
ATOM	733	O	ASP	A	105	33.104	62.102	83.234	1.00	18.61
ATOM	734	CB	ASP	A	105	35.429	59.743	83.951	1.00	16.81
ATOM	735	CG	ASP	A	105	36.831	59.545	84.440	1.00	15.10
ATOM	736	OD1	ASP	A	105	37.573	60.520	84.573	1.00	19.01
ATOM	737	OD2	ASP	A	105	37.177	58.402	84.685	1.00	15.56
ATOM	738	N	ALA	A	106	32.500	60.091	84.096	1.00	15.05
ATOM	739	CA	ALA	A	106	31.111	60.157	83.607	1.00	15.61
ATOM	740	C	ALA	A	106	30.166	61.126	84.315	1.00	19.62
ATOM	741	O	ALA	A	106	29.409	61.881	83.720	1.00	18.83
ATOM	742	CB	ALA	A	106	30.467	58.782	83.682	1.00	11.73
ATOM	743	N	GLY	A	107	30.263	61.102	85.674	1.00	21.49
ATOM	744	CA	GLY	A	107	29.323	61.899	86.503	1.00	16.83
ATOM	745	C	GLY	A	107	29.599	63.356	86.594	1.00	14.80
ATOM	746	O	GLY	A	107	28.714	64.204	86.575	1.00	17.67
ATOM	747	N	ASP	A	108	30.899	63.611	86.662	1.00	16.37
ATOM	748	CA	ASP	A	108	31.305	65.002	86.772	1.00	17.18
ATOM	749	C	ASP	A	108	31.877	65.572	85.485	1.00	18.56
ATOM	750	O	ASP	A	108	31.324	66.472	84.877	1.00	18.77
ATOM	751	CB	ASP	A	108	32.282	65.144	87.947	1.00	16.92
ATOM	752	CG	ASP	A	108	32.862	66.530	88.143	1.00	21.34
ATOM	753	OD1	ASP	A	108	32.247	67.528	87.812	1.00	23.69
ATOM	754	OD2	ASP	A	108	33.983	66.642	88.614	1.00	27.32
ATOM	755	N	LEU	A	109	33.049	65.065	85.107	1.00	18.48
ATOM	756	CA	LEU	A	109	33.814	65.703	84.005	1.00	20.77

FIG. 24

ATOM	757	C	LEU	A	109	32.954	65.922	82.752	1.00	21.46
ATOM	758	O	LEU	A	109	32.905	67.026	82.199	1.00	23.24
ATOM	759	CB	LEU	A	109	35.024	64.826	83.679	1.00	20.60
ATOM	760	CG	LEU	A	109	36.393	65.285	84.113	1.00	21.65
ATOM	761	CD1	LEU	A	109	37.408	64.213	84.096	1.00	17.20
ATOM	762	CD2	LEU	A	109	36.469	66.186	85.254	1.00	20.25
ATOM	763	N	ALA	A	110	32.206	64.812	82.422	1.00	21.81
ATOM	764	CA	ALA	A	110	31.336	64.771	81.215	1.00	20.79
ATOM	765	C	ALA	A	110	30.074	65.608	81.232	1.00	23.23
ATOM	766	O	ALA	A	110	29.504	65.885	80.182	1.00	23.66
ATOM	767	CB	ALA	A	110	30.921	63.333	80.868	1.00	20.49
ATOM	768	N	THR	A	111	29.672	66.038	82.465	1.00	20.15
ATOM	769	CA	THR	A	111	28.453	66.863	82.653	1.00	19.21
ATOM	770	C	THR	A	111	28.654	68.292	83.132	1.00	18.58
ATOM	771	O	THR	A	111	27.754	69.106	83.131	1.00	18.77
ATOM	772	CB	THR	A	111	27.469	66.257	83.628	1.00	18.46
ATOM	773	OG1	THR	A	111	28.011	66.399	84.949	1.00	23.25
ATOM	774	CG2	THR	A	111	27.094	64.802	83.347	1.00	15.78
ATOM	775	N	ARG	A	112	29.870	68.595	83.547	1.00	20.94
ATOM	776	CA	ARG	A	112	30.068	69.805	84.369	1.00	22.62
ATOM	777	C	ARG	A	112	29.745	71.185	83.786	1.00	23.68
ATOM	778	O	ARG	A	112	29.035	72.025	84.325	1.00	21.09
ATOM	779	CB	ARG	A	112	31.512	69.782	84.911	1.00	22.88
ATOM	780	CG	ARG	A	112	31.847	70.852	85.952	1.00	22.67
ATOM	781	CD	ARG	A	112	33.319	70.922	86.319	1.00	18.55
ATOM	782	NE	ARG	A	112	33.831	69.709	86.930	1.00	22.11
ATOM	783	CZ	ARG	A	112	35.138	69.496	86.853	1.00	21.99
ATOM	784	NH1	ARG	A	112	35.949	70.322	86.227	1.00	23.29
ATOM	785	NH2	ARG	A	112	35.623	68.436	87.414	1.00	23.83
ATOM	786	N	SER	A	113	30.323	71.398	82.583	1.00	21.66
ATOM	787	CA	SER	A	113	30.146	72.736	81.981	1.00	19.14
ATOM	788	C	SER	A	113	28.721	73.124	81.629	1.00	20.09
ATOM	789	O	SER	A	113	28.288	74.263	81.806	1.00	23.06
ATOM	790	CB	SER	A	113	31.029	72.919	80.732	1.00	24.64
ATOM	791	OG	SER	A	113	30.812	71.854	79.778	1.00	25.18
ATOM	792	N	ALA	A	114	27.955	72.094	81.186	1.00	19.43
ATOM	793	CA	ALA	A	114	26.510	72.272	80.944	1.00	17.15
ATOM	794	C	ALA	A	114	25.695	72.377	82.247	1.00	16.95
ATOM	795	O	ALA	A	114	24.890	73.293	82.402	1.00	17.79
ATOM	796	CB	ALA	A	114	25.935	71.096	80.117	1.00	15.05
ATOM	797	N	LYS	A	115	25.993	71.462	83.200	1.00	18.76
ATOM	798	CA	LYS	A	115	25.431	71.618	84.559	1.00	20.52
ATOM	799	C	LYS	A	115	25.524	73.029	85.143	1.00	18.24
ATOM	800	O	LYS	A	115	24.535	73.710	85.429	1.00	19.61
ATOM	801	CB	LYS	A	115	26.048	70.606	85.508	1.00	17.41
ATOM	802	CG	LYS	A	115	25.304	69.294	85.482	1.00	22.93
ATOM	803	CD	LYS	A	115	25.867	68.477	86.654	1.00	26.73
ATOM	804	CE	LYS	A	115	25.353	67.039	86.850	1.00	26.14
ATOM	805	NZ	LYS	A	115	23.888	67.023	87.009	1.00	26.36
ATOM	806	N	ASP	A	116	26.784	73.454	85.203	1.00	19.25
ATOM	807	CA	ASP	A	116	27.073	74.739	85.832	1.00	20.02
ATOM	808	C	ASP	A	116	26.589	75.938	85.076	1.00	23.51
ATOM	809	O	ASP	A	116	26.208	76.967	85.612	1.00	24.69
ATOM	810	CB	ASP	A	116	28.573	74.896	86.053	1.00	22.26

FIG. 25

ATOM	811	CG	ASP	A	116	29.203	73.871	87.029	1.00	25.80
ATOM	812	OD1	ASP	A	116	28.502	73.085	87.657	1.00	27.77
ATOM	813	OD2	ASP	A	116	30.431	73.847	87.166	1.00	28.44
ATOM	814	N	HIS	A	117	26.596	75.793	83.741	1.00	23.53
ATOM	815	CA	HIS	A	117	26.022	76.894	82.957	1.00	21.71
ATOM	816	C	HIS	A	117	24.496	77.044	83.026	1.00	20.75
ATOM	817	O	HIS	A	117	23.932	78.108	83.223	1.00	20.51
ATOM	818	CB	HIS	A	117	26.536	76.787	81.501	1.00	22.93
ATOM	819	CG	HIS	A	117	25.987	77.909	80.635	1.00	22.08
ATOM	820	ND1	HIS	A	117	26.531	79.128	80.459	1.00	23.33
ATOM	821	CD2	HIS	A	117	24.824	77.852	79.881	1.00	22.30
ATOM	822	CE1	HIS	A	117	25.741	79.836	79.615	1.00	23.49
ATOM	823	NE2	HIS	A	117	24.693	79.041	79.262	1.00	23.57
ATOM	824	N	TYR	A	118	23.825	75.906	82.825	1.00	19.95
ATOM	825	CA	TYR	A	118	22.363	76.013	82.795	1.00	19.91
ATOM	826	C	TYR	A	118	21.711	76.075	84.159	1.00	22.89
ATOM	827	O	TYR	A	118	20.615	76.596	84.278	1.00	22.53
ATOM	828	CB	TYR	A	118	21.702	74.869	82.020	1.00	18.70
ATOM	829	CG	TYR	A	118	22.112	74.964	80.550	1.00	19.86
ATOM	830	CD1	TYR	A	118	21.604	76.030	79.775	1.00	20.81
ATOM	831	CD2	TYR	A	118	22.998	74.004	80.005	1.00	20.19
ATOM	832	CE1	TYR	A	118	21.964	76.104	78.410	1.00	24.18
ATOM	833	CE2	TYR	A	118	23.393	74.097	78.652	1.00	22.07
ATOM	834	CZ	TYR	A	118	22.841	75.133	77.869	1.00	24.85
ATOM	835	OH	TYR	A	118	23.138	75.231	76.525	1.00	25.02
ATOM	836	N	MET	A	119	22.385	75.453	85.158	1.00	22.72
ATOM	837	CA	MET	A	119	21.795	75.408	86.516	1.00	25.49
ATOM	838	C	MET	A	119	20.328	75.033	86.619	1.00	22.79
ATOM	839	O	MET	A	119	19.526	75.639	87.309	1.00	23.65
ATOM	840	CB	MET	A	119	22.009	76.758	87.200	1.00	31.90
ATOM	841	CG	MET	A	119	23.479	77.200	87.296	1.00	41.79
ATOM	842	SD	MET	A	119	23.683	78.779	88.163	1.00	50.25
ATOM	843	CE	MET	A	119	22.932	79.838	86.910	1.00	48.37
ATOM	844	N	ARG	A	120	19.958	74.021	85.840	1.00	21.05
ATOM	845	CA	ARG	A	120	18.529	73.782	85.704	1.00	19.45
ATOM	846	C	ARG	A	120	17.877	73.247	86.989	1.00	16.34
ATOM	847	O	ARG	A	120	18.483	72.369	87.587	1.00	17.21
ATOM	848	CB	ARG	A	120	18.345	72.757	84.558	1.00	16.25
ATOM	849	CG	ARG	A	120	16.913	72.517	84.063	1.00	17.39
ATOM	850	CD	ARG	A	120	16.775	71.558	82.842	1.00	19.83
ATOM	851	NE	ARG	A	120	15.450	71.636	82.189	1.00	20.39
ATOM	852	CZ	ARG	A	120	14.929	70.642	81.479	1.00	12.14
ATOM	853	NH1	ARG	A	120	15.600	69.574	81.259	1.00	12.74
ATOM	854	NH2	ARG	A	120	13.724	70.767	81.007	1.00	15.75
ATOM	855	N	ILE	A	121	16.676	73.723	87.290	1.00	16.46
ATOM	856	CA	ILE	A	121	15.807	73.186	88.360	1.00	22.91
ATOM	857	C	ILE	A	121	15.258	71.795	88.080	1.00	23.50
ATOM	858	O	ILE	A	121	14.648	71.571	87.043	1.00	26.14
ATOM	859	CB	ILE	A	121	14.594	74.134	88.686	1.00	25.98
ATOM	860	CG1	ILE	A	121	14.986	75.592	88.783	1.00	29.16
ATOM	861	CG2	ILE	A	121	13.793	73.870	89.982	1.00	23.20
ATOM	862	CD1	ILE	A	121	16.075	75.914	89.785	1.00	29.73
ATOM	863	N	ARG	A	122	15.463	70.877	89.036	1.00	21.01
ATOM	864	CA	ARG	A	122	14.883	69.534	88.976	1.00	19.80

FIG. 26

ATOM	865	C	ARG	A	122	13.372	69.532	89.091	1.00	17.61
ATOM	866	O	ARG	A	122	12.805	70.488	89.613	1.00	18.79
ATOM	867	CB	ARG	A	122	15.533	68.653	90.033	1.00	17.47
ATOM	868	CG	ARG	A	122	17.023	68.706	89.841	1.00	18.78
ATOM	869	CD	ARG	A	122	17.721	67.861	90.852	1.00	21.00
ATOM	870	NE	ARG	A	122	19.141	68.121	90.748	1.00	28.80
ATOM	871	CZ	ARG	A	122	19.914	67.081	90.491	1.00	34.31
ATOM	872	NH1	ARG	A	122	19.401	65.871	90.426	1.00	40.28
ATOM	873	NH2	ARG	A	122	21.196	67.257	90.289	1.00	32.47
ATOM	874	N	PRO	A	123	12.700	68.460	88.577	1.00	17.64
ATOM	875	CA	PRO	A	123	11.243	68.461	88.684	1.00	18.56
ATOM	876	C	PRO	A	123	10.668	68.630	90.118	1.00	20.86
ATOM	877	O	PRO	A	123	9.881	69.536	90.331	1.00	20.65
ATOM	878	CB	PRO	A	123	10.808	67.150	88.004	1.00	16.86
ATOM	879	CG	PRO	A	123	12.028	66.572	87.296	1.00	15.55
ATOM	880	CD	PRO	A	123	13.235	67.291	87.881	1.00	15.48
ATOM	881	N	PHE	A	124	11.077	67.771	91.105	1.00	21.82
ATOM	882	CA	PHE	A	124	10.489	67.948	92.468	1.00	20.01
ATOM	883	C	PHE	A	124	10.541	69.394	93.016	1.00	16.73
ATOM	884	O	PHE	A	124	9.581	69.970	93.486	1.00	17.82
ATOM	885	CB	PHE	A	124	11.044	66.869	93.422	1.00	17.84
ATOM	886	CG	PHE	A	124	12.484	67.199	93.795	1.00	19.87
ATOM	887	CD1	PHE	A	124	12.748	68.117	94.850	1.00	20.96
ATOM	888	CD2	PHE	A	124	13.554	66.632	93.075	1.00	19.87
ATOM	889	CE1	PHE	A	124	14.068	68.524	95.134	1.00	21.78
ATOM	890	CE2	PHE	A	124	14.881	67.014	93.381	1.00	21.98
ATOM	891	CZ	PHE	A	124	15.129	67.975	94.386	1.00	23.27
ATOM	892	N	ALA	A	125	11.681	70.039	92.775	1.00	18.30
ATOM	893	CA	ALA	A	125	11.866	71.464	93.089	1.00	20.06
ATOM	894	C	ALA	A	125	11.033	72.481	92.291	1.00	24.90
ATOM	895	O	ALA	A	125	10.455	73.445	92.789	1.00	24.77
ATOM	896	CB	ALA	A	125	13.358	71.840	92.990	1.00	16.96
ATOM	897	N	PHE	A	126	10.941	72.202	90.977	1.00	23.91
ATOM	898	CA	PHE	A	126	10.017	72.958	90.145	1.00	22.66
ATOM	899	C	PHE	A	126	8.590	72.919	90.692	1.00	20.74
ATOM	900	O	PHE	A	126	7.910	73.945	90.785	1.00	21.66
ATOM	901	CB	PHE	A	126	10.051	72.379	88.705	1.00	19.61
ATOM	902	CG	PHE	A	126	9.147	73.140	87.765	1.00	16.99
ATOM	903	CD1	PHE	A	126	9.669	74.211	87.022	1.00	15.15
ATOM	904	CD2	PHE	A	126	7.794	72.757	87.656	1.00	17.75
ATOM	905	CE1	PHE	A	126	8.824	74.913	86.144	1.00	14.16
ATOM	906	CE2	PHE	A	126	6.940	73.472	86.799	1.00	17.56
ATOM	907	CZ	PHE	A	126	7.471	74.538	86.048	1.00	12.93
ATOM	908	N	TYR	A	127	8.183	71.664	91.002	1.00	20.13
ATOM	909	CA	TYR	A	127	6.843	71.414	91.525	1.00	20.41
ATOM	910	C	TYR	A	127	6.642	71.689	93.032	1.00	24.41
ATOM	911	O	TYR	A	127	5.525	71.665	93.532	1.00	23.70
ATOM	912	CB	TYR	A	127	6.370	69.994	91.207	1.00	20.85
ATOM	913	CG	TYR	A	127	6.198	69.850	89.697	1.00	25.51
ATOM	914	CD1	TYR	A	127	7.200	69.185	88.947	1.00	27.02
ATOM	915	CD2	TYR	A	127	5.064	70.407	89.065	1.00	25.24
ATOM	916	CE1	TYR	A	127	7.057	69.037	87.552	1.00	28.75
ATOM	917	CE2	TYR	A	127	4.907	70.261	87.663	1.00	28.24
ATOM	918	CZ	TYR	A	127	5.891	69.543	86.936	1.00	28.76

FIG. 27

ATOM	919	OH	TYR	A	127	5.716	69.314	85.588	1.00	27.53
ATOM	920	N	GLY	A	128	7.764	71.960	93.723	1.00	23.74
ATOM	921	CA	GLY	A	128	7.675	72.217	95.170	1.00	24.88
ATOM	922	C	GLY	A	128	7.138	71.011	95.924	1.00	24.57
ATOM	923	O	GLY	A	128	6.383	71.095	96.866	1.00	29.82
ATOM	924	N	VAL	A	129	7.527	69.854	95.426	1.00	24.16
ATOM	925	CA	VAL	A	129	7.144	68.604	96.044	1.00	23.21
ATOM	926	C	VAL	A	129	8.377	67.802	96.358	1.00	24.99
ATOM	927	O	VAL	A	129	9.529	68.188	96.189	1.00	25.90
ATOM	928	CB	VAL	A	129	6.193	67.776	95.187	1.00	22.38
ATOM	929	CG1	VAL	A	129	6.738	67.390	93.815	1.00	17.75
ATOM	930	CG2	VAL	A	129	4.895	68.549	95.125	1.00	24.52
ATOM	931	N	SER	A	130	8.089	66.617	96.832	1.00	25.98
ATOM	932	CA	SER	A	130	9.242	65.724	96.973	1.00	29.71
ATOM	933	C	SER	A	130	9.322	64.672	95.895	1.00	29.73
ATOM	934	O	SER	A	130	8.403	64.485	95.103	1.00	30.28
ATOM	935	CB	SER	A	130	9.183	64.999	98.309	1.00	35.36
ATOM	936	OG	SER	A	130	7.964	64.244	98.427	1.00	41.61
ATOM	937	N	THR	A	131	10.440	63.952	95.934	1.00	30.35
ATOM	938	CA	THR	A	131	10.533	62.819	94.996	1.00	27.90
ATOM	939	C	THR	A	131	9.733	61.569	95.361	1.00	28.80
ATOM	940	O	THR	A	131	9.051	61.508	96.366	1.00	30.16
ATOM	941	CB	THR	A	131	11.996	62.471	94.783	1.00	26.62
ATOM	942	OG1	THR	A	131	12.500	61.841	95.953	1.00	29.21
ATOM	943	CG2	THR	A	131	12.839	63.682	94.446	1.00	19.32
ATOM	944	N	CYS	A	132	9.835	60.528	94.551	1.00	27.12
ATOM	945	CA	CYS	A	132	9.203	59.271	94.996	1.00	27.75
ATOM	946	C	CYS	A	132	9.911	58.540	96.137	1.00	28.96
ATOM	947	O	CYS	A	132	9.556	57.487	96.634	1.00	28.80
ATOM	948	CB	CYS	A	132	9.081	58.274	93.831	1.00	24.68
ATOM	949	SG	CYS	A	132	10.538	57.273	93.459	1.00	24.12
ATOM	950	N	ASN	A	133	11.021	59.158	96.447	1.00	33.31
ATOM	951	CA	ASN	A	133	12.012	58.492	97.236	1.00	39.44
ATOM	952	C	ASN	A	133	12.008	58.776	98.750	1.00	45.19
ATOM	953	O	ASN	A	133	12.269	57.928	99.583	1.00	50.38
ATOM	954	CB	ASN	A	133	13.285	58.876	96.522	1.00	35.83
ATOM	955	CG	ASN	A	133	14.294	57.823	96.731	1.00	37.18
ATOM	956	OD1	ASN	A	133	15.478	58.059	96.663	1.00	38.83
ATOM	957	ND2	ASN	A	133	13.815	56.623	97.017	1.00	42.51
ATOM	958	N	THR	A	134	11.642	59.993	99.118	1.00	48.69
ATOM	959	CA	THR	A	134	12.585	61.110	98.925	1.00	56.17
ATOM	960	C	THR	A	134	13.935	61.171	99.735	1.00	61.49
ATOM	961	OCT1	THR	A	134	14.052	60.565	100.816	1.00	66.36
ATOM	962	OCT2	THR	A	134	14.937	61.779	99.291	1.00	63.18
ATOM	963	CB	THR	A	134	11.704	62.374	98.968	1.00	56.04
ATOM	964	OG1	THR	A	134	12.306	63.614	98.469	1.00	56.23
ATOM	965	CG2	THR	A	134	10.869	62.400	100.243	1.00	53.77
ATOM	966	N	GLN	A	137	16.953	60.437	100.819	1.00100.00
ATOM	967	CA	GLN	A	137	17.845	60.498	102.027	1.00	99.78
ATOM	968	C	GLN	A	137	19.036	61.512	102.211	1.00	98.61
ATOM	969	O	GLN	A	137	19.386	61.891	103.324	1.00	97.54
ATOM	970	CB	GLN	A	137	18.343	59.083	102.397	1.00100.00
ATOM	971	CG	GLN	A	137	17.669	58.407	103.615	1.00	99.38
ATOM	972	CD	GLN	A	137	18.060	59.017	104.963	1.00	98.64

FIG. 28

ATOM	973	OE1	GLN	A	137	17.484	58.784	106.009	1.00	98.03
ATOM	974	NE2	GLN	A	137	19.086	59.847	104.972	1.00	100.00
ATOM	975	N	ASP	A	138	19.627	61.949	101.081	1.00	97.91
ATOM	976	CA	ASP	A	138	20.479	63.151	101.162	1.00	95.99
ATOM	977	C	ASP	A	138	19.761	64.494	101.063	1.00	93.86
ATOM	978	O	ASP	A	138	18.589	64.579	100.711	1.00	92.76
ATOM	979	CB	ASP	A	138	21.585	63.102	100.115	1.00	97.46
ATOM	980	CG	ASP	A	138	22.893	62.963	100.866	1.00	100.00
ATOM	981	OD1	ASP	A	138	23.371	61.842	101.028	1.00	100.00
ATOM	982	OD2	ASP	A	138	23.432	63.969	101.333	1.00	100.00
ATOM	983	N	LYS	A	139	20.494	65.564	101.380	1.00	92.69
ATOM	984	CA	LYS	A	139	19.813	66.855	101.218	1.00	91.50
ATOM	985	C	LYS	A	139	19.719	67.313	99.775	1.00	88.92
ATOM	986	O	LYS	A	139	20.557	68.082	99.308	1.00	89.47
ATOM	987	CB	LYS	A	139	20.464	67.987	102.010	1.00	94.21
ATOM	988	CG	LYS	A	139	19.574	69.246	102.020	1.00	96.82
ATOM	989	CD	LYS	A	139	20.362	70.569	102.123	1.00	99.43
ATOM	990	CE	LYS	A	139	20.785	71.241	100.793	1.00	100.00
ATOM	991	NZ	LYS	A	139	21.686	70.402	99.978	1.00	100.00
ATOM	992	N	LEU	A	140	18.654	66.828	99.114	1.00	85.87
ATOM	993	CA	LEU	A	140	18.426	67.018	97.660	1.00	79.60
ATOM	994	C	LEU	A	140	18.772	68.392	97.043	1.00	75.62
ATOM	995	O	LEU	A	140	18.242	69.442	97.416	1.00	75.74
ATOM	996	CB	LEU	A	140	16.981	66.620	97.283	1.00	77.27
ATOM	997	CG	LEU	A	140	16.640	65.142	97.462	1.00	74.31
ATOM	998	CD1	LEU	A	140	17.569	64.263	96.645	1.00	73.21
ATOM	999	CD2	LEU	A	140	15.178	64.838	97.167	1.00	73.91
ATOM	1000	N	SER	A	141	19.713	68.357	96.067	1.00	70.08
ATOM	1001	CA	SER	A	141	19.868	69.619	95.320	1.00	64.86
ATOM	1002	C	SER	A	141	18.713	69.941	94.396	1.00	61.18
ATOM	1003	O	SER	A	141	18.189	69.080	93.708	1.00	61.77
ATOM	1004	CB	SER	A	141	21.127	69.682	94.461	1.00	64.49
ATOM	1005	OG	SER	A	141	21.354	71.028	94.002	1.00	66.43
ATOM	1006	N	LYS	A	142	18.349	71.235	94.379	1.00	57.81
ATOM	1007	CA	LYS	A	142	17.238	71.661	93.493	1.00	54.35
ATOM	1008	C	LYS	A	142	17.498	71.829	91.964	1.00	45.94
ATOM	1009	O	LYS	A	142	16.615	72.091	91.202	1.00	40.89
ATOM	1010	CB	LYS	A	142	16.631	72.953	94.061	1.00	57.69
ATOM	1011	CG	LYS	A	142	17.518	74.222	93.959	1.00	62.63
ATOM	1012	CD	LYS	A	142	16.625	75.420	93.545	1.00	68.07
ATOM	1013	CE	LYS	A	142	17.200	76.856	93.475	1.00	71.28
ATOM	1014	NZ	LYS	A	142	16.136	77.844	93.162	1.00	70.88
ATOM	1015	N	ASN	A	143	18.772	71.719	91.611	1.00	45.99
ATOM	1016	CA	ASN	A	143	19.527	72.392	90.538	1.00	44.71
ATOM	1017	C	ASN	A	143	20.592	71.481	89.878	1.00	42.57
ATOM	1018	O	ASN	A	143	20.794	70.322	90.283	1.00	40.17
ATOM	1019	CB	ASN	A	143	20.343	73.547	91.124	1.00	50.34
ATOM	1020	CG	ASN	A	143	19.624	74.818	90.876	1.00	55.19
ATOM	1021	OD1	ASN	A	143	18.441	74.944	91.098	1.00	59.21
ATOM	1022	ND2	ASN	A	143	20.366	75.786	90.389	1.00	59.88
ATOM	1023	N	GLY	A	144	21.265	72.084	88.819	1.00	39.72
ATOM	1024	CA	GLY	A	144	22.264	71.401	87.958	1.00	26.74
ATOM	1025	C	GLY	A	144	21.691	70.105	87.407	1.00	21.44
ATOM	1026	O	GLY	A	144	22.343	69.071	87.322	1.00	25.78

FIG. 29

ATOM	1027	N	SER	A	145	20.380	70.181	87.105	1.00	19.15
ATOM	1028	CA	SER	A	145	19.590	69.023	86.596	1.00	20.14
ATOM	1029	C	SER	A	145	20.077	68.461	85.223	1.00	20.58
ATOM	1030	O	SER	A	145	20.121	67.279	84.943	1.00	21.22
ATOM	1031	CB	SER	A	145	18.171	69.499	86.338	1.00	18.89
ATOM	1032	OG	SER	A	145	17.219	68.526	86.712	1.00	28.02
ATOM	1033	N	TYR	A	146	20.531	69.419	84.399	1.00	22.70
ATOM	1034	CA	TYR	A	146	20.867	69.170	82.968	1.00	19.51
ATOM	1035	C	TYR	A	146	22.366	69.260	82.633	1.00	16.00
ATOM	1036	O	TYR	A	146	22.930	70.339	82.736	1.00	17.85
ATOM	1037	CB	TYR	A	146	20.097	70.216	82.114	1.00	18.79
ATOM	1038	CG	TYR	A	146	20.211	69.933	80.600	1.00	20.29
ATOM	1039	CD1	TYR	A	146	19.310	69.027	80.015	1.00	19.58
ATOM	1040	CD2	TYR	A	146	21.205	70.582	79.824	1.00	20.42
ATOM	1041	CE1	TYR	A	146	19.389	68.781	78.631	1.00	23.13
ATOM	1042	CE2	TYR	A	146	21.287	70.337	78.424	1.00	21.68
ATOM	1043	CZ	TYR	A	146	20.349	69.449	77.849	1.00	20.03
ATOM	1044	OH	TYR	A	146	20.320	69.236	76.483	1.00	21.40
ATOM	1045	N	PRO	A	147	22.994	68.144	82.187	1.00	16.52
ATOM	1046	CA	PRO	A	147	22.385	66.793	82.188	1.00	17.87
ATOM	1047	C	PRO	A	147	22.496	66.069	83.580	1.00	20.67
ATOM	1048	O	PRO	A	147	23.198	66.531	84.480	1.00	22.35
ATOM	1049	CB	PRO	A	147	23.250	66.107	81.122	1.00	15.36
ATOM	1050	CG	PRO	A	147	24.649	66.716	81.297	1.00	15.06
ATOM	1051	CD	PRO	A	147	24.356	68.168	81.630	1.00	16.28
ATOM	1052	N	SER	A	148	21.827	64.908	83.662	1.00	18.73
ATOM	1053	CA	SER	A	148	21.951	64.019	84.823	1.00	19.51
ATOM	1054	C	SER	A	148	23.269	63.281	84.930	1.00	19.93
ATOM	1055	O	SER	A	148	23.601	62.439	84.108	1.00	20.09
ATOM	1056	CB	SER	A	148	20.828	62.997	84.807	1.00	18.55
ATOM	1057	OG	SER	A	148	20.990	61.966	85.780	1.00	19.29
ATOM	1058	N	GLY	A	149	24.036	63.618	85.972	1.00	18.26
ATOM	1059	CA	GLY	A	149	25.284	62.888	86.231	1.00	16.00
ATOM	1060	C	GLY	A	149	25.096	61.411	86.577	1.00	19.38
ATOM	1061	O	GLY	A	149	25.791	60.549	86.044	1.00	21.04
ATOM	1062	N	HIS	A	150	24.085	61.096	87.427	1.00	20.25
ATOM	1063	CA	HIS	A	150	23.690	59.680	87.624	1.00	19.01
ATOM	1064	C	HIS	A	150	23.381	58.861	86.330	1.00	19.93
ATOM	1065	O	HIS	A	150	23.833	57.725	86.145	1.00	20.78
ATOM	1066	CB	HIS	A	150	22.507	59.533	88.619	1.00	18.01
ATOM	1067	CG	HIS	A	150	22.162	58.068	88.909	1.00	20.60
ATOM	1068	ND1	HIS	A	150	22.864	57.235	89.730	1.00	23.41
ATOM	1069	CD2	HIS	A	150	21.117	57.313	88.374	1.00	21.91
ATOM	1070	CE1	HIS	A	150	22.287	55.996	89.732	1.00	22.83
ATOM	1071	NE2	HIS	A	150	21.220	56.051	88.893	1.00	24.19
ATOM	1072	N	THR	A	151	22.593	59.482	85.432	1.00	18.98
ATOM	1073	CA	THR	A	151	22.325	58.814	84.132	1.00	17.17
ATOM	1074	C	THR	A	151	23.548	58.652	83.228	1.00	13.61
ATOM	1075	O	THR	A	151	23.814	57.594	82.659	1.00	17.00
ATOM	1076	CB	THR	A	151	21.270	59.590	83.407	1.00	16.57
ATOM	1077	OG1	THR	A	151	20.137	59.738	84.258	1.00	18.00
ATOM	1078	CG2	THR	A	151	20.898	58.983	82.045	1.00	13.22
ATOM	1079	N	SER	A	152	24.361	59.722	83.197	1.00	14.30
ATOM	1080	CA	SER	A	152	25.687	59.598	82.557	1.00	15.99

FIG. 30

ATOM	1081	C	SER	A	152	26.575	58.446	83.029	1.00	19.72
ATOM	1082	O	SER	A	152	27.086	57.628	82.255	1.00	17.38
ATOM	1083	CB	SER	A	152	26.434	60.927	82.644	1.00	12.58
ATOM	1084	OG	SER	A	152	27.648	60.861	81.911	1.00	16.08
ATOM	1085	N	ILE	A	153	26.662	58.340	84.403	1.00	20.60
ATOM	1086	CA	ILE	A	153	27.272	57.121	85.017	1.00	16.15
ATOM	1087	C	ILE	A	153	26.622	55.802	84.631	1.00	10.76
ATOM	1088	O	ILE	A	153	27.293	54.850	84.262	1.00	14.38
ATOM	1089	CB	ILE	A	153	27.384	57.170	86.608	1.00	15.02
ATOM	1090	CG1	ILE	A	153	28.187	58.421	86.963	1.00	16.37
ATOM	1091	CG2	ILE	A	153	28.154	55.944	87.164	1.00	12.98
ATOM	1092	CD1	ILE	A	153	27.870	59.034	88.338	1.00	16.58
ATOM	1093	N	GLY	A	154	25.285	55.763	84.720	1.00	9.72
ATOM	1094	CA	GLY	A	154	24.662	54.476	84.397	1.00	13.63
ATOM	1095	C	GLY	A	154	24.843	54.033	82.910	1.00	16.00
ATOM	1096	O	GLY	A	154	25.022	52.866	82.571	1.00	16.37
ATOM	1097	N	TRP	A	155	24.801	55.047	82.025	1.00	16.77
ATOM	1098	CA	TRP	A	155	24.960	54.747	80.589	1.00	16.73
ATOM	1099	C	TRP	A	155	26.378	54.351	80.200	1.00	15.90
ATOM	1100	O	TRP	A	155	26.656	53.301	79.628	1.00	18.41
ATOM	1101	CB	TRP	A	155	24.442	55.940	79.771	1.00	16.52
ATOM	1102	CG	TRP	A	155	24.320	55.475	78.321	1.00	19.11
ATOM	1103	CD1	TRP	A	155	25.009	56.015	77.210	1.00	18.94
ATOM	1104	CD2	TRP	A	155	23.471	54.426	77.765	1.00	18.98
ATOM	1105	NE1	TRP	A	155	24.679	55.352	76.044	1.00	17.77
ATOM	1106	CE2	TRP	A	155	23.781	54.322	76.357	1.00	22.22
ATOM	1107	CE3	TRP	A	155	22.585	53.486	78.337	1.00	19.43
ATOM	1108	CZ2	TRP	A	155	23.084	53.377	75.564	1.00	17.99
ATOM	1109	CZ3	TRP	A	155	21.913	52.538	77.537	1.00	19.46
ATOM	1110	CH2	TRP	A	155	22.191	52.464	76.158	1.00	17.84
ATOM	1111	N	ALA	A	156	27.299	55.209	80.623	1.00	15.37
ATOM	1112	CA	ALA	A	156	28.702	54.836	80.515	1.00	14.36
ATOM	1113	C	ALA	A	156	29.156	53.503	81.108	1.00	19.46
ATOM	1114	O	ALA	A	156	29.895	52.723	80.528	1.00	19.86
ATOM	1115	CB	ALA	A	156	29.564	55.918	81.136	1.00	15.83
ATOM	1116	N	THR	A	157	28.651	53.207	82.327	1.00	19.95
ATOM	1117	CA	THR	A	157	28.820	51.832	82.831	1.00	17.52
ATOM	1118	C	THR	A	157	28.177	50.744	81.994	1.00	15.22
ATOM	1119	O	THR	A	157	28.825	49.745	81.765	1.00	19.09
ATOM	1120	CB	THR	A	157	28.328	51.667	84.291	1.00	14.92
ATOM	1121	OG1	THR	A	157	28.932	52.679	85.054	1.00	18.29
ATOM	1122	CG2	THR	A	157	28.620	50.327	84.944	1.00	13.21
ATOM	1123	N	ALA	A	158	26.930	50.947	81.535	1.00	14.63
ATOM	1124	CA	ALA	A	158	26.365	49.936	80.621	1.00	17.10
ATOM	1125	C	ALA	A	158	27.213	49.686	79.354	1.00	15.52
ATOM	1126	O	ALA	A	158	27.539	48.565	79.025	1.00	16.52
ATOM	1127	CB	ALA	A	158	24.942	50.300	80.203	1.00	13.99
ATOM	1128	N	LEU	A	159	27.655	50.766	78.705	1.00	17.91
ATOM	1129	CA	LEU	A	159	28.613	50.615	77.580	1.00	17.69
ATOM	1130	C	LEU	A	159	29.895	49.851	77.846	1.00	19.93
ATOM	1131	O	LEU	A	159	30.277	48.954	77.092	1.00	19.21
ATOM	1132	CB	LEU	A	159	28.959	51.971	76.939	1.00	14.08
ATOM	1133	CG	LEU	A	159	27.744	52.759	76.396	1.00	11.97
ATOM	1134	CD1	LEU	A	159	27.045	52.105	75.210	1.00	12.90

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FIG. 31

ATOM	1135	CD2	LEU	A	159	28.177	54.158	76.046	1.00	12.40
ATOM	1136	N	VAL	A	160	30.547	50.181	79.014	1.00	21.70
ATOM	1137	CA	VAL	A	160	31.713	49.315	79.310	1.00	20.85
ATOM	1138	C	VAL	A	160	31.429	47.877	79.767	1.00	21.33
ATOM	1139	O	VAL	A	160	32.086	46.918	79.409	1.00	20.74
ATOM	1140	CB	VAL	A	160	32.574	50.032	80.367	1.00	21.59
ATOM	1141	CG1	VAL	A	160	33.518	49.143	81.174	1.00	20.11
ATOM	1142	CG2	VAL	A	160	33.299	51.307	79.977	1.00	20.10
ATOM	1143	N	LEU	A	161	30.351	47.711	80.542	1.00	21.86
ATOM	1144	CA	LEU	A	161	29.850	46.366	80.838	1.00	20.50
ATOM	1145	C	LEU	A	161	29.462	45.490	79.613	1.00	23.16
ATOM	1146	O	LEU	A	161	29.753	44.294	79.564	1.00	22.89
ATOM	1147	CB	LEU	A	161	28.623	46.472	81.733	1.00	18.65
ATOM	1148	CG	LEU	A	161	28.685	46.438	83.262	1.00	20.99
ATOM	1149	CD1	LEU	A	161	27.473	46.378	84.194	1.00	21.43
ATOM	1150	CD2	LEU	A	161	29.729	45.492	83.855	1.00	19.30
ATOM	1151	N	ALA	A	162	28.755	46.146	78.648	1.00	21.20
ATOM	1152	CA	ALA	A	162	28.384	45.496	77.361	1.00	19.14
ATOM	1153	C	ALA	A	162	29.591	44.948	76.586	1.00	17.15
ATOM	1154	O	ALA	A	162	29.620	43.812	76.133	1.00	20.85
ATOM	1155	CB	ALA	A	162	27.581	46.464	76.500	1.00	17.38
ATOM	1156	N	GLU	A	163	30.663	45.745	76.603	1.00	14.74
ATOM	1157	CA	GLU	A	163	31.962	45.262	76.118	1.00	17.48
ATOM	1158	C	GLU	A	163	32.648	44.080	76.824	1.00	22.07
ATOM	1159	O	GLU	A	163	33.271	43.216	76.227	1.00	23.96
ATOM	1160	CB	GLU	A	163	32.915	46.448	76.000	1.00	13.52
ATOM	1161	CG	GLU	A	163	34.227	46.018	75.359	1.00	13.04
ATOM	1162	CD	GLU	A	163	35.240	47.119	75.338	1.00	15.88
ATOM	1163	OE1	GLU	A	163	36.427	46.814	75.269	1.00	19.78
ATOM	1164	OE2	GLU	A	163	34.873	48.290	75.377	1.00	20.10
ATOM	1165	N	ILE	A	164	32.504	44.039	78.153	1.00	20.17
ATOM	1166	CA	ILE	A	164	32.996	42.869	78.905	1.00	18.72
ATOM	1167	C	ILE	A	164	32.164	41.609	78.757	1.00	17.39
ATOM	1168	O	ILE	A	164	32.635	40.481	78.674	1.00	20.44
ATOM	1169	CB	ILE	A	164	33.132	43.293	80.382	1.00	20.67
ATOM	1170	CG1	ILE	A	164	34.222	44.361	80.452	1.00	18.83
ATOM	1171	CG2	ILE	A	164	33.398	42.110	81.345	1.00	20.70
ATOM	1172	CD1	ILE	A	164	34.144	45.084	81.793	1.00	21.31
ATOM	1173	N	ASN	A	165	30.869	41.846	78.704	1.00	18.41
ATOM	1174	CA	ASN	A	165	29.979	40.712	78.524	1.00	21.36
ATOM	1175	C	ASN	A	165	28.957	40.867	77.375	1.00	23.74
ATOM	1176	O	ASN	A	165	27.753	40.988	77.563	1.00	23.14
ATOM	1177	CB	ASN	A	165	29.324	40.404	79.878	1.00	21.69
ATOM	1178	CG	ASN	A	165	28.471	39.156	79.861	1.00	25.72
ATOM	1179	OD1	ASN	A	165	28.469	38.307	78.967	1.00	29.37
ATOM	1180	ND2	ASN	A	165	27.730	39.051	80.951	1.00	27.39
ATOM	1181	N	PRO	A	166	29.466	40.814	76.118	1.00	25.93
ATOM	1182	CA	PRO	A	166	28.556	40.971	74.957	1.00	26.27
ATOM	1183	C	PRO	A	166	27.447	39.924	74.837	1.00	24.06
ATOM	1184	O	PRO	A	166	26.361	40.184	74.360	1.00	24.11
ATOM	1185	CB	PRO	A	166	29.517	41.040	73.781	1.00	25.15
ATOM	1186	CG	PRO	A	166	30.731	40.254	74.255	1.00	27.68
ATOM	1187	CD	PRO	A	166	30.849	40.613	75.728	1.00	24.89
ATOM	1188	N	GLN	A	167	27.679	38.741	75.385	1.00	25.15

FIG. 32

ATOM	1189	CA	GLN	A	167	26.552	37.804	75.508	1.00	27.09
ATOM	1190	C	GLN	A	167	25.275	38.321	76.189	1.00	25.06
ATOM	1191	O	GLN	A	167	24.162	37.932	75.883	1.00	23.75
ATOM	1192	CB	GLN	A	167	27.080	36.617	76.282	1.00	35.50
ATOM	1193	CG	GLN	A	167	27.386	35.380	75.468	1.00	52.12
ATOM	1194	CD	GLN	A	167	26.074	34.747	75.000	1.00	65.78
ATOM	1195	OE1	GLN	A	167	25.950	34.245	73.889	1.00	72.02
ATOM	1196	NE2	GLN	A	167	25.047	34.780	75.867	1.00	71.50
ATOM	1197	N	ARG	A	168	25.513	39.242	77.156	1.00	26.04
ATOM	1198	CA	ARG	A	168	24.389	39.900	77.837	1.00	25.63
ATOM	1199	C	ARG	A	168	24.242	41.368	77.558	1.00	23.88
ATOM	1200	O	ARG	A	168	23.632	42.106	78.308	1.00	24.09
ATOM	1201	CB	ARG	A	168	24.452	39.638	79.337	1.00	24.63
ATOM	1202	CG	ARG	A	168	24.087	38.171	79.408	1.00	25.72
ATOM	1203	CD	ARG	A	168	23.986	37.617	80.802	1.00	33.72
ATOM	1204	NE	ARG	A	168	22.970	38.302	81.587	1.00	35.38
ATOM	1205	CZ	ARG	A	168	21.729	37.877	81.680	1.00	35.91
ATOM	1206	NH1	ARG	A	168	20.908	38.482	82.490	1.00	34.99
ATOM	1207	NH2	ARG	A	168	21.314	36.867	80.975	1.00	39.28
ATOM	1208	N	GLN	A	169	24.838	41.810	76.424	1.00	23.22
ATOM	1209	CA	GLN	A	169	24.820	43.228	76.080	1.00	19.99
ATOM	1210	C	GLN	A	169	23.441	43.850	76.067	1.00	21.38
ATOM	1211	O	GLN	A	169	23.216	44.969	76.492	1.00	24.60
ATOM	1212	CB	GLN	A	169	25.571	43.510	74.769	1.00	22.07
ATOM	1213	CG	GLN	A	169	24.970	42.878	73.494	1.00	20.93
ATOM	1214	CD	GLN	A	169	25.716	43.287	72.207	1.00	23.42
ATOM	1215	OE1	GLN	A	169	26.680	44.055	72.202	1.00	24.82
ATOM	1216	NE2	GLN	A	169	25.186	42.738	71.109	1.00	13.86
ATOM	1217	N	ASN	A	170	22.455	43.089	75.600	1.00	20.48
ATOM	1218	CA	ASN	A	170	21.138	43.736	75.525	1.00	20.97
ATOM	1219	C	ASN	A	170	20.484	44.007	76.892	1.00	19.73
ATOM	1220	O	ASN	A	170	19.852	45.020	77.128	1.00	18.90
ATOM	1221	CB	ASN	A	170	20.195	42.930	74.595	1.00	24.43
ATOM	1222	CG	ASN	A	170	20.763	42.881	73.153	1.00	25.82
ATOM	1223	OD1	ASN	A	170	20.842	43.862	72.440	1.00	26.22
ATOM	1224	ND2	ASN	A	170	21.197	41.709	72.734	1.00	25.47
ATOM	1225	N	GLU	A	171	20.680	43.042	77.790	1.00	21.27
ATOM	1226	CA	GLU	A	171	20.166	43.146	79.157	1.00	19.84
ATOM	1227	C	GLU	A	171	20.849	44.220	79.926	1.00	16.23
ATOM	1228	O	GLU	A	171	20.199	45.026	80.575	1.00	20.87
ATOM	1229	CB	GLU	A	171	20.317	41.822	79.892	1.00	20.47
ATOM	1230	CG	GLU	A	171	19.412	40.750	79.312	1.00	24.15
ATOM	1231	CD	GLU	A	171	20.157	39.825	78.376	1.00	26.37
ATOM	1232	OE1	GLU	A	171	21.076	40.256	77.685	1.00	23.54
ATOM	1233	OE2	GLU	A	171	19.801	38.645	78.363	1.00	32.14
ATOM	1234	N	ILE	A	172	22.169	44.236	79.751	1.00	17.53
ATOM	1235	CA	ILE	A	172	23.029	45.318	80.257	1.00	16.90
ATOM	1236	C	ILE	A	172	22.679	46.733	79.813	1.00	20.21
ATOM	1237	O	ILE	A	172	22.454	47.636	80.617	1.00	18.91
ATOM	1238	CB	ILE	A	172	24.507	44.992	79.956	1.00	17.00
ATOM	1239	CG1	ILE	A	172	25.000	43.685	80.613	1.00	15.78
ATOM	1240	CG2	ILE	A	172	25.426	46.163	80.300	1.00	18.13
ATOM	1241	CD1	ILE	A	172	26.426	43.320	80.163	1.00	13.83
ATOM	1242	N	LEU	A	173	22.575	46.909	78.468	1.00	20.75

FIG. 33

ATOM	1243	CA	LEU	A	173	22.107	48.206	77.946	1.00	17.70
ATOM	1244	C	LEU	A	173	20.699	48.622	78.396	1.00	16.26
ATOM	1245	O	LEU	A	173	20.376	49.774	78.663	1.00	18.18
ATOM	1246	CB	LEU	A	173	22.176	48.201	76.419	1.00	16.81
ATOM	1247	CG	LEU	A	173	23.600	48.021	75.966	1.00	18.73
ATOM	1248	CD1	LEU	A	173	24.410	49.282	76.138	1.00	16.97
ATOM	1249	CD2	LEU	A	173	23.619	47.550	74.505	1.00	23.91
ATOM	1250	N	LYS	A	174	19.835	47.625	78.475	1.00	15.86
ATOM	1251	CA	LYS	A	174	18.494	47.970	78.945	1.00	19.21
ATOM	1252	C	LYS	A	174	18.453	48.415	80.429	1.00	21.86
ATOM	1253	O	LYS	A	174	17.800	49.404	80.737	1.00	20.00
ATOM	1254	CB	LYS	A	174	17.577	46.773	78.700	1.00	20.19
ATOM	1255	CG	LYS	A	174	16.094	47.130	78.731	1.00	27.84
ATOM	1256	CD	LYS	A	174	15.799	48.368	77.858	1.00	36.14
ATOM	1257	CE	LYS	A	174	14.309	48.628	77.774	1.00	40.56
ATOM	1258	NZ	LYS	A	174	13.775	48.622	79.156	1.00	49.45
ATOM	1259	N	ARG	A	175	19.250	47.698	81.286	1.00	21.93
ATOM	1260	CA	ARG	A	175	19.476	48.145	82.686	1.00	19.65
ATOM	1261	C	ARG	A	175	20.037	49.561	82.807	1.00	16.70
ATOM	1262	O	ARG	A	175	19.476	50.419	83.468	1.00	18.12
ATOM	1263	CB	ARG	A	175	20.345	47.126	83.467	1.00	21.25
ATOM	1264	CG	ARG	A	175	20.608	47.477	84.954	1.00	22.00
ATOM	1265	CD	ARG	A	175	19.259	47.669	85.656	1.00	25.63
ATOM	1266	NE	ARG	A	175	19.435	47.923	87.095	1.00	29.77
ATOM	1267	CZ	ARG	A	175	18.601	48.672	87.834	1.00	27.58
ATOM	1268	NH1	ARG	A	175	17.550	49.301	87.355	1.00	24.74
ATOM	1269	NH2	ARG	A	175	18.792	48.780	89.073	1.00	27.45
ATOM	1270	N	GLY	A	176	21.122	49.800	82.048	1.00	17.53
ATOM	1271	CA	GLY	A	176	21.698	51.143	81.893	1.00	17.18
ATOM	1272	C	GLY	A	176	20.679	52.214	81.552	1.00	21.18
ATOM	1273	O	GLY	A	176	20.582	53.278	82.149	1.00	21.85
ATOM	1274	N	TYR	A	177	19.847	51.887	80.547	1.00	22.48
ATOM	1275	CA	TYR	A	177	18.756	52.787	80.117	1.00	20.51
ATOM	1276	C	TYR	A	177	17.754	53.106	81.242	1.00	18.92
ATOM	1277	O	TYR	A	177	17.406	54.246	81.542	1.00	15.84
ATOM	1278	CB	TYR	A	177	18.007	52.120	78.939	1.00	23.76
ATOM	1279	CG	TYR	A	177	17.210	53.131	78.177	1.00	24.47
ATOM	1280	CD1	TYR	A	177	15.817	53.306	78.397	1.00	26.61
ATOM	1281	CD2	TYR	A	177	17.941	53.869	77.236	1.00	29.40
ATOM	1282	CE1	TYR	A	177	15.139	54.308	77.661	1.00	29.08
ATOM	1283	CE2	TYR	A	177	17.270	54.855	76.515	1.00	30.70
ATOM	1284	CZ	TYR	A	177	15.899	55.092	76.747	1.00	32.01
ATOM	1285	OH	TYR	A	177	15.401	56.167	76.020	1.00	41.52
ATOM	1286	N	GLU	A	178	17.354	52.008	81.867	1.00	19.45
ATOM	1287	CA	GLU	A	178	16.429	52.094	82.972	1.00	22.02
ATOM	1288	C	GLU	A	178	16.820	52.802	84.236	1.00	20.09
ATOM	1289	O	GLU	A	178	16.001	53.492	84.805	1.00	21.41
ATOM	1290	CB	GLU	A	178	16.010	50.731	83.357	1.00	25.45
ATOM	1291	CG	GLU	A	178	15.173	50.032	82.303	1.00	34.73
ATOM	1292	CD	GLU	A	178	13.893	50.810	81.951	1.00	40.36
ATOM	1293	OE1	GLU	A	178	13.432	51.667	82.707	1.00	33.51
ATOM	1294	OE2	GLU	A	178	13.352	50.556	80.876	1.00	45.77
ATOM	1295	N	LEU	A	179	18.090	52.695	84.609	1.00	19.63
ATOM	1296	CA	LEU	A	179	18.655	53.567	85.665	1.00	19.10

FIG. 34

ATOM	1297	C	LEU	A	179	18.366	55.051	85.511	1.00	20.25
ATOM	1298	O	LEU	A	179	17.838	55.726	86.374	1.00	19.26
ATOM	1299	CB	LEU	A	179	20.178	53.361	85.813	1.00	17.45
ATOM	1300	CG	LEU	A	179	20.610	52.013	86.426	1.00	18.23
ATOM	1301	CD1	LEU	A	179	20.093	51.829	87.873	1.00	16.98
ATOM	1302	CD2	LEU	A	179	22.124	51.811	86.340	1.00	16.34
ATOM	1303	N	GLY	A	180	18.647	55.545	84.290	1.00	19.84
ATOM	1304	CA	GLY	A	180	18.171	56.903	83.987	1.00	15.90
ATOM	1305	C	GLY	A	180	16.655	57.072	84.027	1.00	17.05
ATOM	1306	O	GLY	A	180	16.130	58.031	84.564	1.00	19.49
ATOM	1307	N	GLN	A	181	15.923	56.068	83.478	1.00	18.19
ATOM	1308	CA	GLN	A	181	14.448	56.207	83.522	1.00	17.92
ATOM	1309	C	GLN	A	181	13.822	56.265	84.938	1.00	18.20
ATOM	1310	O	GLN	A	181	12.903	57.008	85.258	1.00	19.66
ATOM	1311	CB	GLN	A	181	13.716	55.189	82.620	1.00	15.39
ATOM	1312	CG	GLN	A	181	13.936	55.324	81.073	1.00	15.18
ATOM	1313	CD	GLN	A	181	13.823	56.763	80.634	1.00	13.30
ATOM	1314	OE1	GLN	A	181	14.769	57.400	80.176	1.00	17.23
ATOM	1315	NE2	GLN	A	181	12.626	57.300	80.812	1.00	12.82
ATOM	1316	N	SER	A	182	14.440	55.497	85.821	1.00	20.03
ATOM	1317	CA	SER	A	182	14.156	55.600	87.273	1.00	16.56
ATOM	1318	C	SER	A	182	14.209	56.973	87.871	1.00	14.78
ATOM	1319	O	SER	A	182	13.305	57.369	88.582	1.00	19.49
ATOM	1320	CB	SER	A	182	15.056	54.630	88.021	1.00	15.31
ATOM	1321	OG	SER	A	182	14.563	53.332	87.714	1.00	16.70
ATOM	1322	N	ARG	A	183	15.246	57.738	87.523	1.00	16.99
ATOM	1323	CA	ARG	A	183	15.289	59.169	87.858	1.00	15.54
ATOM	1324	C	ARG	A	183	14.161	60.085	87.309	1.00	19.55
ATOM	1325	O	ARG	A	183	13.693	61.039	87.956	1.00	17.04
ATOM	1326	CB	ARG	A	183	16.661	59.785	87.569	1.00	14.08
ATOM	1327	CG	ARG	A	183	17.811	59.024	88.265	1.00	19.49
ATOM	1328	CD	ARG	A	183	17.716	59.007	89.816	1.00	21.46
ATOM	1329	NE	ARG	A	183	18.519	57.930	90.434	1.00	22.16
ATOM	1330	CZ	ARG	A	183	19.509	58.121	91.300	1.00	19.15
ATOM	1331	NH1	ARG	A	183	19.913	59.335	91.541	1.00	16.50
ATOM	1332	NH2	ARG	A	183	20.042	57.081	91.914	1.00	18.34
ATOM	1333	N	VAL	A	184	13.681	59.704	86.076	1.00	21.38
ATOM	1334	CA	VAL	A	184	12.494	60.417	85.589	1.00	19.02
ATOM	1335	C	VAL	A	184	11.194	60.051	86.301	1.00	16.98
ATOM	1336	O	VAL	A	184	10.468	60.913	86.800	1.00	18.45
ATOM	1337	CB	VAL	A	184	12.368	60.194	84.070	1.00	19.28
ATOM	1338	CG1	VAL	A	184	11.057	60.717	83.486	1.00	17.84
ATOM	1339	CG2	VAL	A	184	13.517	60.605	83.169	1.00	15.69
ATOM	1340	N	ILE	A	185	10.977	58.734	86.408	1.00	17.32
ATOM	1341	CA	ILE	A	185	9.834	58.241	87.202	1.00	21.14
ATOM	1342	C	ILE	A	185	9.790	58.797	88.672	1.00	22.77
ATOM	1343	O	ILE	A	185	8.749	59.230	89.142	1.00	22.95
ATOM	1344	CB	ILE	A	185	9.810	56.695	87.193	1.00	20.65
ATOM	1345	CG1	ILE	A	185	9.555	56.195	85.758	1.00	18.43
ATOM	1346	CG2	ILE	A	185	8.776	56.133	88.202	1.00	18.29
ATOM	1347	CD1	ILE	A	185	9.914	54.734	85.494	1.00	14.60
ATOM	1348	N	CYS	A	186	10.976	58.837	89.332	1.00	20.34
ATOM	1349	CA	CYS	A	186	11.005	59.262	90.745	1.00	21.26
ATOM	1350	C	CYS	A	186	10.979	60.766	90.931	1.00	22.80

FIG. 35

ATOM	1351	O	CYS	A	186	10.775	61.304	92.009	1.00	23.98
ATOM	1352	CB	CYS	A	186	12.220	58.669	91.429	1.00	21.60
ATOM	1353	SG	CYS	A	186	12.075	58.576	93.237	1.00	25.16
ATOM	1354	N	GLY	A	187	11.149	61.494	89.814	1.00	20.34
ATOM	1355	CA	GLY	A	187	11.023	62.949	89.981	1.00	13.75
ATOM	1356	C	GLY	A	187	12.351	63.676	90.197	1.00	14.55
ATOM	1357	O	GLY	A	187	12.436	64.871	90.453	1.00	16.08
ATOM	1358	N	TYR	A	188	13.434	62.894	90.072	1.00	14.86
ATOM	1359	CA	TYR	A	188	14.736	63.526	90.226	1.00	16.85
ATOM	1360	C	TYR	A	188	15.214	64.366	89.046	1.00	20.24
ATOM	1361	O	TYR	A	188	15.979	65.318	89.192	1.00	18.42
ATOM	1362	CB	TYR	A	188	15.758	62.441	90.479	1.00	21.64
ATOM	1363	CG	TYR	A	188	15.683	61.913	91.899	1.00	27.20
ATOM	1364	CD1	TYR	A	188	16.748	62.226	92.737	1.00	32.00
ATOM	1365	CD2	TYR	A	188	14.604	61.128	92.365	1.00	30.81
ATOM	1366	CE1	TYR	A	188	16.727	61.784	94.071	1.00	35.38
ATOM	1367	CE2	TYR	A	188	14.570	60.695	93.705	1.00	30.65
ATOM	1368	CZ	TYR	A	188	15.624	61.071	94.556	1.00	35.88
ATOM	1369	OH	TYR	A	188	15.607	60.787	95.912	1.00	41.39
ATOM	1370	N	HIS	A	189	14.751	63.890	87.862	1.00	19.35
ATOM	1371	CA	HIS	A	189	15.215	64.475	86.589	1.00	19.83
ATOM	1372	C	HIS	A	189	14.108	64.550	85.551	1.00	16.85
ATOM	1373	O	HIS	A	189	13.232	63.689	85.533	1.00	18.10
ATOM	1374	CB	HIS	A	189	16.360	63.648	86.032	1.00	15.43
ATOM	1375	CG	HIS	A	189	17.677	64.142	86.589	1.00	16.05
ATOM	1376	ND1	HIS	A	189	18.154	65.384	86.414	1.00	17.24
ATOM	1377	CD2	HIS	A	189	18.581	63.433	87.382	1.00	17.58
ATOM	1378	CE1	HIS	A	189	19.347	65.503	87.080	1.00	16.38
ATOM	1379	NE2	HIS	A	189	19.587	64.304	87.667	1.00	18.68
ATOM	1380	N	TRP	A	190	14.183	65.611	84.723	1.00	18.99
ATOM	1381	CA	TRP	A	190	13.341	65.719	83.490	1.00	17.22
ATOM	1382	C	TRP	A	190	13.768	64.690	82.453	1.00	15.79
ATOM	1383	O	TRP	A	190	14.942	64.354	82.416	1.00	15.77
ATOM	1384	CB	TRP	A	190	13.502	67.102	82.855	1.00	16.12
ATOM	1385	CG	TRP	A	190	13.134	68.178	83.857	1.00	12.39
ATOM	1386	CD1	TRP	A	190	14.033	69.073	84.454	1.00	10.88
ATOM	1387	CD2	TRP	A	190	11.800	68.581	84.295	1.00	14.35
ATOM	1388	NE1	TRP	A	190	13.343	69.989	85.186	1.00	13.77
ATOM	1389	CE2	TRP	A	190	11.976	69.731	85.141	1.00	10.71
ATOM	1390	CE3	TRP	A	190	10.505	68.036	84.094	1.00	14.68
ATOM	1391	CZ2	TRP	A	190	10.845	70.401	85.666	1.00	12.89
ATOM	1392	CZ3	TRP	A	190	9.393	68.700	84.672	1.00	16.93
ATOM	1393	CH2	TRP	A	190	9.557	69.875	85.441	1.00	12.82
ATOM	1394	N	GLN	A	191	12.859	64.188	81.613	1.00	16.92
ATOM	1395	CA	GLN	A	191	13.316	63.234	80.569	1.00	17.49
ATOM	1396	C	GLN	A	191	14.519	63.720	79.696	1.00	15.64
ATOM	1397	O	GLN	A	191	15.508	63.054	79.429	1.00	16.52
ATOM	1398	CB	GLN	A	191	12.113	62.829	79.721	1.00	15.28
ATOM	1399	CG	GLN	A	191	12.522	61.832	78.632	1.00	17.26
ATOM	1400	CD	GLN	A	191	12.860	60.493	79.206	1.00	16.84
ATOM	1401	OE1	GLN	A	191	12.086	59.920	79.946	1.00	21.21
ATOM	1402	NE2	GLN	A	191	14.027	59.971	78.864	1.00	16.69
ATOM	1403	N	SER	A	192	14.448	65.016	79.389	1.00	17.04
ATOM	1404	CA	SER	A	192	15.564	65.622	78.666	1.00	15.81

F I G. 36

ATOM	1405	C	SER	A	192	16.899	65.683	79.339	1.00	17.61
ATOM	1406	O	SER	A	192	17.937	65.640	78.700	1.00	16.65
ATOM	1407	CB	SER	A	192	15.209	67.005	78.211	1.00	15.87
ATOM	1408	OG	SER	A	192	14.862	67.833	79.313	1.00	21.12
ATOM	1409	N	ASP	A	193	16.886	65.712	80.681	1.00	17.44
ATOM	1410	CA	ASP	A	193	18.190	65.648	81.360	1.00	15.23
ATOM	1411	C	ASP	A	193	18.889	64.316	81.197	1.00	12.26
ATOM	1412	O	ASP	A	193	20.113	64.204	81.054	1.00	14.16
ATOM	1413	CB	ASP	A	193	18.036	65.832	82.887	1.00	16.01
ATOM	1414	CG	ASP	A	193	17.367	67.116	83.311	1.00	14.57
ATOM	1415	OD1	ASP	A	193	17.503	68.180	82.691	1.00	15.89
ATOM	1416	OD2	ASP	A	193	16.673	67.038	84.312	1.00	19.14
ATOM	1417	N	VAL	A	194	18.025	63.283	81.216	1.00	11.48
ATOM	1418	CA	VAL	A	194	18.425	61.882	81.108	1.00	13.18
ATOM	1419	C	VAL	A	194	18.851	61.478	79.663	1.00	15.63
ATOM	1420	O	VAL	A	194	19.852	60.822	79.387	1.00	15.79
ATOM	1421	CB	VAL	A	194	17.210	61.135	81.625	1.00	16.33
ATOM	1422	CG1	VAL	A	194	17.152	61.202	83.184	1.00	19.26
ATOM	1423	CG2	VAL	A	194	17.079	59.712	81.106	1.00	17.70
ATOM	1424	N	ASP	A	195	18.050	61.992	78.728	1.00	16.54
ATOM	1425	CA	ASP	A	195	18.488	61.921	77.332	1.00	16.55
ATOM	1426	C	ASP	A	195	19.801	62.636	77.029	1.00	14.74
ATOM	1427	O	ASP	A	195	20.758	62.076	76.519	1.00	18.92
ATOM	1428	CB	ASP	A	195	17.367	62.455	76.477	1.00	15.91
ATOM	1429	CG	ASP	A	195	16.139	61.563	76.560	1.00	19.86
ATOM	1430	OD1	ASP	A	195	16.153	60.385	76.922	1.00	27.62
ATOM	1431	OD2	ASP	A	195	15.090	62.069	76.264	1.00	26.20
ATOM	1432	N	ALA	A	196	19.902	63.900	77.450	1.00	15.85
ATOM	1433	CA	ALA	A	196	21.203	64.555	77.312	1.00	14.73
ATOM	1434	C	ALA	A	196	22.383	63.806	77.932	1.00	18.85
ATOM	1435	O	ALA	A	196	23.512	63.751	77.429	1.00	21.06
ATOM	1436	CB	ALA	A	196	21.134	65.950	77.904	1.00	13.59
ATOM	1437	N	ALA	A	197	22.056	63.177	79.091	1.00	19.14
ATOM	1438	CA	ALA	A	197	23.098	62.442	79.808	1.00	17.62
ATOM	1439	C	ALA	A	197	23.644	61.202	79.090	1.00	17.71
ATOM	1440	O	ALA	A	197	24.851	60.931	79.104	1.00	18.18
ATOM	1441	CB	ALA	A	197	22.587	62.002	81.181	1.00	15.91
ATOM	1442	N	ARG	A	198	22.711	60.477	78.418	1.00	16.04
ATOM	1443	CA	ARG	A	198	23.238	59.409	77.565	1.00	15.41
ATOM	1444	C	ARG	A	198	24.179	59.843	76.413	1.00	14.99
ATOM	1445	O	ARG	A	198	25.194	59.219	76.113	1.00	17.07
ATOM	1446	CB	ARG	A	198	22.136	58.469	77.080	1.00	14.50
ATOM	1447	CG	ARG	A	198	21.195	58.043	78.179	1.00	16.67
ATOM	1448	CD	ARG	A	198	20.142	57.044	77.730	1.00	19.20
ATOM	1449	NE	ARG	A	198	19.280	56.629	78.849	1.00	22.72
ATOM	1450	CZ	ARG	A	198	18.003	57.012	79.061	1.00	22.30
ATOM	1451	NH1	ARG	A	198	17.412	57.905	78.325	1.00	20.95
ATOM	1452	NH2	ARG	A	198	17.292	56.518	80.045	1.00	21.57
ATOM	1453	N	VAL	A	199	23.907	61.030	75.842	1.00	17.69
ATOM	1454	CA	VAL	A	199	24.961	61.510	74.913	1.00	17.44
ATOM	1455	C	VAL	A	199	26.376	61.736	75.457	1.00	18.48
ATOM	1456	O	VAL	A	199	27.360	61.145	74.988	1.00	19.25
ATOM	1457	CB	VAL	A	199	24.452	62.820	74.284	1.00	15.93
ATOM	1458	CG1	VAL	A	199	25.350	63.540	73.279	1.00	11.45

FIG. 37

ATOM	1459	CG2	VAL	A	199	23.072	62.640	73.680	1.00	15.33
ATOM	1460	N	VAL	A	200	26.471	62.548	76.550	1.00	18.52
ATOM	1461	CA	VAL	A	200	27.822	62.723	77.153	1.00	16.27
ATOM	1462	C	VAL	A	200	28.442	61.461	77.794	1.00	14.37
ATOM	1463	O	VAL	A	200	29.643	61.247	77.797	1.00	17.25
ATOM	1464	CB	VAL	A	200	27.811	63.938	78.100	1.00	16.56
ATOM	1465	CG1	VAL	A	200	26.761	63.894	79.246	1.00	13.52
ATOM	1466	CG2	VAL	A	200	27.666	65.177	77.226	1.00	17.14
ATOM	1467	N	GLY	A	201	27.556	60.570	78.283	1.00	14.98
ATOM	1468	CA	GLY	A	201	27.998	59.297	78.836	1.00	13.20
ATOM	1469	C	GLY	A	201	28.609	58.377	77.824	1.00	16.81
ATOM	1470	O	GLY	A	201	29.588	57.701	78.067	1.00	17.03
ATOM	1471	N	SER	A	202	28.034	58.413	76.614	1.00	17.82
ATOM	1472	CA	SER	A	202	28.757	57.750	75.509	1.00	16.70
ATOM	1473	C	SER	A	202	30.087	58.390	75.104	1.00	13.91
ATOM	1474	O	SER	A	202	31.117	57.765	74.939	1.00	18.47
ATOM	1475	CB	SER	A	202	27.813	57.511	74.303	1.00	15.94
ATOM	1476	OG	SER	A	202	27.634	58.737	73.600	1.00	19.26
ATOM	1477	N	ALA	A	203	30.094	59.719	75.030	1.00	14.76
ATOM	1478	CA	ALA	A	203	31.333	60.383	74.641	1.00	14.41
ATOM	1479	C	ALA	A	203	32.527	60.110	75.563	1.00	17.92
ATOM	1480	O	ALA	A	203	33.652	59.803	75.177	1.00	16.36
ATOM	1481	CB	ALA	A	203	31.042	61.872	74.572	1.00	13.61
ATOM	1482	N	VAL	A	204	32.200	60.126	76.880	1.00	18.27
ATOM	1483	CA	VAL	A	204	33.290	59.835	77.823	1.00	16.45
ATOM	1484	C	VAL	A	204	33.834	58.394	77.718	1.00	13.88
ATOM	1485	O	VAL	A	204	35.015	58.177	77.916	1.00	17.64
ATOM	1486	CB	VAL	A	204	32.893	60.245	79.285	1.00	16.63
ATOM	1487	CG1	VAL	A	204	34.131	60.323	80.177	1.00	16.51
ATOM	1488	CG2	VAL	A	204	31.836	59.301	79.862	1.00	13.53
ATOM	1489	N	VAL	A	205	32.971	57.392	77.355	1.00	15.31
ATOM	1490	CA	VAL	A	205	33.648	56.100	77.152	1.00	17.30
ATOM	1491	C	VAL	A	205	34.636	56.018	75.953	1.00	19.20
ATOM	1492	O	VAL	A	205	35.644	55.311	76.002	1.00	19.08
ATOM	1493	CB	VAL	A	205	32.563	55.014	77.035	1.00	19.10
ATOM	1494	CG1	VAL	A	205	32.812	53.549	76.681	1.00	16.51
ATOM	1495	CG2	VAL	A	205	31.797	55.088	78.343	1.00	17.27
ATOM	1496	N	ALA	A	206	34.409	56.893	74.934	1.00	21.03
ATOM	1497	CA	ALA	A	206	35.452	57.018	73.888	1.00	19.17
ATOM	1498	C	ALA	A	206	36.765	57.498	74.469	1.00	19.27
ATOM	1499	O	ALA	A	206	37.809	56.868	74.353	1.00	18.59
ATOM	1500	CB	ALA	A	206	34.982	57.988	72.809	1.00	16.60
ATOM	1501	N	THR	A	207	36.643	58.597	75.234	1.00	20.20
ATOM	1502	CA	THR	A	207	37.873	59.078	75.903	1.00	20.52
ATOM	1503	C	THR	A	207	38.613	58.126	76.838	1.00	21.84
ATOM	1504	O	THR	A	207	39.831	58.030	76.898	1.00	23.45
ATOM	1505	CB	THR	A	207	37.659	60.341	76.674	1.00	19.84
ATOM	1506	OG1	THR	A	207	36.577	61.100	76.137	1.00	20.11
ATOM	1507	CG2	THR	A	207	38.945	61.141	76.710	1.00	21.15
ATOM	1508	N	LEU	A	208	37.806	57.345	77.574	1.00	23.89
ATOM	1509	CA	LEU	A	208	38.323	56.332	78.510	1.00	22.19
ATOM	1510	C	LEU	A	208	39.165	55.285	77.783	1.00	25.28
ATOM	1511	O	LEU	A	208	40.232	54.880	78.228	1.00	24.41
ATOM	1512	CB	LEU	A	208	37.170	55.700	79.312	1.00	21.93

FIG. 38

ATOM	1513	CG	LEU	A	208	36.238	56.370	80.325	1.00	24.99
ATOM	1514	CD1	LEU	A	208	35.117	55.631	81.058	1.00	26.55
ATOM	1515	CD2	LEU	A	208	37.303	56.685	81.377	1.00	22.67
ATOM	1516	N	HIS	A	209	38.666	54.873	76.588	1.00	24.64
ATOM	1517	CA	HIS	A	209	39.495	53.970	75.766	1.00	20.81
ATOM	1518	C	HIS	A	209	40.863	54.530	75.277	1.00	19.15
ATOM	1519	O	HIS	A	209	41.807	53.872	74.934	1.00	20.30
ATOM	1520	CB	HIS	A	209	38.656	53.449	74.595	1.00	16.87
ATOM	1521	CG	HIS	A	209	37.588	52.476	74.994	1.00	13.42
ATOM	1522	ND1	HIS	A	209	36.335	52.782	75.375	1.00	14.12
ATOM	1523	CD2	HIS	A	209	37.686	51.099	74.975	1.00	12.37
ATOM	1524	CE1	HIS	A	209	35.653	51.616	75.586	1.00	10.36
ATOM	1525	NE2	HIS	A	209	36.493	50.590	75.334	1.00	13.53
ATOM	1526	N	THR	A	210	41.035	55.827	75.336	1.00	20.82
ATOM	1527	CA	THR	A	210	42.393	56.384	75.116	1.00	21.40
ATOM	1528	C	THR	A	210	43.396	56.387	76.298	1.00	26.34
ATOM	1529	O	THR	A	210	44.567	56.745	76.188	1.00	27.83
ATOM	1530	CB	THR	A	210	42.315	57.836	74.662	1.00	22.02
ATOM	1531	OG1	THR	A	210	42.096	58.723	75.795	1.00	25.04
ATOM	1532	CG2	THR	A	210	41.307	58.070	73.528	1.00	20.46
ATOM	1533	N	ASN	A	211	42.844	56.032	77.482	1.00	26.32
ATOM	1534	CA	ASN	A	211	43.544	56.135	78.782	1.00	23.64
ATOM	1535	C	ASN	A	211	44.212	54.824	79.204	1.00	20.62
ATOM	1536	O	ASN	A	211	43.591	53.785	79.374	1.00	22.28
ATOM	1537	CB	ASN	A	211	42.563	56.749	79.827	1.00	24.99
ATOM	1538	CG	ASN	A	211	43.226	56.863	81.206	1.00	24.09
ATOM	1539	OD1	ASN	A	211	43.320	55.886	81.935	1.00	25.25
ATOM	1540	ND2	ASN	A	211	43.689	58.038	81.566	1.00	21.24
ATOM	1541	N	PRO	A	212	45.563	54.884	79.353	1.00	22.01
ATOM	1542	CA	PRO	A	212	46.337	53.660	79.633	1.00	21.52
ATOM	1543	C	PRO	A	212	45.859	52.883	80.848	1.00	22.52
ATOM	1544	O	PRO	A	212	45.670	51.673	80.882	1.00	22.12
ATOM	1545	CB	PRO	A	212	47.743	54.190	79.845	1.00	22.52
ATOM	1546	CG	PRO	A	212	47.805	55.535	79.117	1.00	25.40
ATOM	1547	CD	PRO	A	212	46.391	56.076	79.175	1.00	22.01
ATOM	1548	N	ALA	A	213	45.626	53.674	81.897	1.00	23.96
ATOM	1549	CA	ALA	A	213	45.139	53.025	83.140	1.00	23.57
ATOM	1550	C	ALA	A	213	43.797	52.337	83.019	1.00	21.76
ATOM	1551	O	ALA	A	213	43.600	51.185	83.403	1.00	24.96
ATOM	1552	CB	ALA	A	213	45.039	54.071	84.259	1.00	21.55
ATOM	1553	N	PHE	A	214	42.885	53.085	82.373	1.00	19.30
ATOM	1554	CA	PHE	A	214	41.617	52.431	82.017	1.00	20.02
ATOM	1555	C	PHE	A	214	41.798	51.170	81.197	1.00	20.38
ATOM	1556	O	PHE	A	214	41.255	50.120	81.510	1.00	18.82
ATOM	1557	CB	PHE	A	214	40.690	53.445	81.314	1.00	23.58
ATOM	1558	CG	PHE	A	214	39.367	52.839	80.840	1.00	26.35
ATOM	1559	CD1	PHE	A	214	38.249	52.765	81.711	1.00	24.66
ATOM	1560	CD2	PHE	A	214	39.262	52.365	79.507	1.00	23.08
ATOM	1561	CE1	PHE	A	214	37.032	52.191	81.265	1.00	27.05
ATOM	1562	CE2	PHE	A	214	38.052	51.792	79.077	1.00	19.74
ATOM	1563	CZ	PHE	A	214	36.951	51.697	79.944	1.00	22.04
ATOM	1564	N	GLN	A	215	42.654	51.298	80.149	1.00	22.02
ATOM	1565	CA	GLN	A	215	42.904	50.137	79.275	1.00	21.33
ATOM	1566	C	GLN	A	215	43.354	48.889	79.995	1.00	21.73

FIG. 39

ATOM	1567	O	GLN	A	215	42.823	47.783	79.875	1.00	21.17
ATOM	1568	CB	GLN	A	215	43.970	50.520	78.278	1.00	22.37
ATOM	1569	CG	GLN	A	215	43.483	51.517	77.261	1.00	22.30
ATOM	1570	CD	GLN	A	215	44.662	52.026	76.479	1.00	28.18
ATOM	1571	OE1	GLN	A	215	45.821	51.695	76.664	1.00	32.27
ATOM	1572	NE2	GLN	A	215	44.359	52.947	75.605	1.00	28.35
ATOM	1573	N	GLN	A	216	44.375	49.154	80.845	1.00	24.60
ATOM	1574	CA	GLN	A	216	44.876	48.089	81.718	1.00	25.81
ATOM	1575	C	GLN	A	216	43.909	47.530	82.715	1.00	23.07
ATOM	1576	O	GLN	A	216	43.822	46.328	82.899	1.00	22.91
ATOM	1577	CB	GLN	A	216	46.052	48.544	82.517	1.00	33.78
ATOM	1578	CG	GLN	A	216	47.181	49.037	81.631	1.00	49.94
ATOM	1579	CD	GLN	A	216	48.161	49.693	82.574	1.00	61.57
ATOM	1580	OE1	GLN	A	216	48.354	49.243	83.704	1.00	69.34
ATOM	1581	NE2	GLN	A	216	48.737	50.805	82.114	1.00	63.50
ATOM	1582	N	GLN	A	217	43.155	48.439	83.377	1.00	22.58
ATOM	1583	CA	GLN	A	217	42.099	47.917	84.261	1.00	23.69
ATOM	1584	C	GLN	A	217	40.971	47.113	83.590	1.00	24.92
ATOM	1585	O	GLN	A	217	40.480	46.102	84.088	1.00	24.09
ATOM	1586	CB	GLN	A	217	41.565	49.042	85.189	1.00	23.44
ATOM	1587	CG	GLN	A	217	40.720	48.541	86.407	1.00	23.24
ATOM	1588	CD	GLN	A	217	41.489	47.589	87.335	1.00	21.58
ATOM	1589	OE1	GLN	A	217	42.676	47.749	87.598	1.00	24.82
ATOM	1590	NE2	GLN	A	217	40.827	46.516	87.744	1.00	19.85
ATOM	1591	N	LEU	A	218	40.628	47.595	82.390	1.00	26.00
ATOM	1592	CA	LEU	A	218	39.701	46.859	81.532	1.00	23.47
ATOM	1593	C	LEU	A	218	40.195	45.495	81.093	1.00	21.96
ATOM	1594	O	LEU	A	218	39.476	44.515	81.209	1.00	22.51
ATOM	1595	CB	LEU	A	218	39.309	47.724	80.327	1.00	23.65
ATOM	1596	CG	LEU	A	218	38.292	47.073	79.369	1.00	21.04
ATOM	1597	CD1	LEU	A	218	38.103	47.980	78.168	1.00	25.30
ATOM	1598	CD2	LEU	A	218	36.952	46.736	80.004	1.00	13.22
ATOM	1599	N	GLN	A	219	41.451	45.425	80.640	1.00	23.49
ATOM	1600	CA	GLN	A	219	42.033	44.079	80.457	1.00	29.37
ATOM	1601	C	GLN	A	219	41.880	43.156	81.681	1.00	29.60
ATOM	1602	O	GLN	A	219	41.455	42.016	81.569	1.00	29.63
ATOM	1603	CB	GLN	A	219	43.544	44.131	80.199	1.00	37.46
ATOM	1604	CG	GLN	A	219	44.052	44.703	78.867	1.00	51.74
ATOM	1605	CD	GLN	A	219	45.511	45.267	78.911	1.00	60.29
ATOM	1606	OE1	GLN	A	219	46.415	44.774	79.568	1.00	65.45
ATOM	1607	NE2	GLN	A	219	45.764	46.352	78.161	1.00	60.81
ATOM	1608	N	LYS	A	220	42.206	43.722	82.879	1.00	28.28
ATOM	1609	CA	LYS	A	220	42.004	42.926	84.111	1.00	26.68
ATOM	1610	C	LYS	A	220	40.588	42.446	84.386	1.00	24.54
ATOM	1611	O	LYS	A	220	40.347	41.275	84.640	1.00	26.87
ATOM	1612	CB	LYS	A	220	42.591	43.631	85.319	1.00	29.93
ATOM	1613	CG	LYS	A	220	44.019	43.952	84.934	1.00	36.96
ATOM	1614	CD	LYS	A	220	45.015	44.044	86.081	1.00	47.54
ATOM	1615	CE	LYS	A	220	44.741	45.121	87.121	1.00	55.28
ATOM	1616	NZ	LYS	A	220	44.868	46.456	86.510	1.00	61.92
ATOM	1617	N	ALA	A	221	39.630	43.379	84.217	1.00	21.04
ATOM	1618	CA	ALA	A	221	38.215	42.960	84.307	1.00	18.69
ATOM	1619	C	ALA	A	221	37.761	41.903	83.291	1.00	24.31
ATOM	1620	O	ALA	A	221	37.095	40.921	83.598	1.00	26.78

FIG. 40

ATOM	1621	CB	ALA	A	221	37.306	44.177	84.140	1.00	14.85
ATOM	1622	N	LYS	A	222	38.223	42.106	82.029	1.00	24.15
ATOM	1623	CA	LYS	A	222	38.065	41.018	81.046	1.00	23.96
ATOM	1624	C	LYS	A	222	38.668	39.675	81.431	1.00	22.61
ATOM	1625	O	LYS	A	222	38.023	38.628	81.422	1.00	21.88
ATOM	1626	CB	LYS	A	222	38.591	41.444	79.659	1.00	22.92
ATOM	1627	CG	LYS	A	222	37.682	42.516	79.109	1.00	22.76
ATOM	1628	CD	LYS	A	222	38.038	42.903	77.691	1.00	22.50
ATOM	1629	CE	LYS	A	222	37.050	43.918	77.109	1.00	22.07
ATOM	1630	NZ	LYS	A	222	37.556	44.613	75.909	1.00	21.47
ATOM	1631	N	ALA	A	223	39.949	39.728	81.830	1.00	22.84
ATOM	1632	CA	ALA	A	223	40.533	38.472	82.353	1.00	25.17
ATOM	1633	C	ALA	A	223	39.812	37.842	83.543	1.00	26.19
ATOM	1634	O	ALA	A	223	39.534	36.652	83.573	1.00	27.99
ATOM	1635	CB	ALA	A	223	42.013	38.638	82.691	1.00	21.36
ATOM	1636	N	GLU	A	224	39.424	38.696	84.487	1.00	27.72
ATOM	1637	CA	GLU	A	224	38.643	38.187	85.610	1.00	27.59
ATOM	1638	C	GLU	A	224	37.338	37.525	85.191	1.00	28.89
ATOM	1639	O	GLU	A	224	36.971	36.412	85.568	1.00	28.75
ATOM	1640	CB	GLU	A	224	38.476	39.348	86.606	1.00	29.18
ATOM	1641	CG	GLU	A	224	37.470	39.099	87.741	1.00	29.05
ATOM	1642	CD	GLU	A	224	37.335	40.348	88.557	1.00	29.41
ATOM	1643	OE1	GLU	A	224	36.506	41.189	88.269	1.00	28.08
ATOM	1644	OE2	GLU	A	224	38.060	40.487	89.516	1.00	31.14
ATOM	1645	N	PHE	A	225	36.659	38.233	84.288	1.00	29.33
ATOM	1646	CA	PHE	A	225	35.398	37.699	83.770	1.00	28.70
ATOM	1647	C	PHE	A	225	35.551	36.354	83.061	1.00	31.53
ATOM	1648	O	PHE	A	225	34.802	35.399	83.222	1.00	29.17
ATOM	1649	CB	PHE	A	225	34.786	38.756	82.858	1.00	26.48
ATOM	1650	CG	PHE	A	225	33.449	38.281	82.361	1.00	25.90
ATOM	1651	CD1	PHE	A	225	32.361	38.258	83.250	1.00	28.71
ATOM	1652	CD2	PHE	A	225	33.317	37.854	81.022	1.00	28.64
ATOM	1653	CE1	PHE	A	225	31.129	37.758	82.817	1.00	29.98
ATOM	1654	CE2	PHE	A	225	32.074	37.365	80.564	1.00	28.53
ATOM	1655	CZ	PHE	A	225	30.998	37.309	81.479	1.00	30.02
ATOM	1656	N	ALA	A	226	36.635	36.308	82.289	1.00	31.91
ATOM	1657	CA	ALA	A	226	36.996	35.055	81.643	1.00	36.17
ATOM	1658	C	ALA	A	226	37.178	33.829	82.536	1.00	40.94
ATOM	1659	O	ALA	A	226	36.704	32.735	82.271	1.00	41.75
ATOM	1660	CB	ALA	A	226	38.284	35.261	80.877	1.00	33.81
ATOM	1661	N	GLN	A	227	37.883	34.081	83.647	1.00	44.91
ATOM	1662	CA	GLN	A	227	38.067	32.931	84.543	1.00	49.32
ATOM	1663	C	GLN	A	227	36.782	32.579	85.233	1.00	51.62
ATOM	1664	O	GLN	A	227	36.396	31.467	85.528	1.00	50.02
ATOM	1665	CB	GLN	A	227	39.239	33.150	85.499	1.00	50.80
ATOM	1666	CG	GLN	A	227	40.441	33.937	84.900	1.00	59.92
ATOM	1667	CD	GLN	A	227	40.812	33.681	83.397	1.00	68.68
ATOM	1668	OE1	GLN	A	227	40.799	32.592	82.834	1.00	73.97
ATOM	1669	NE2	GLN	A	227	41.221	34.764	82.726	1.00	65.71
ATOM	1670	N	HIS	A	228	36.041	33.669	85.411	1.00	58.91
ATOM	1671	CA	HIS	A	228	34.687	33.501	85.925	1.00	65.53
ATOM	1672	C	HIS	A	228	33.816	32.519	85.143	1.00	68.04
ATOM	1673	O	HIS	A	228	33.014	31.764	85.662	1.00	67.46
ATOM	1674	CB	HIS	A	228	34.091	34.903	86.045	1.00	68.11

FIG. 41

ATOM	1675	CG	HIS	A	228	32.632	34.780	86.283	1.00	71.87
ATOM	1676	ND1	HIS	A	228	31.729	34.968	85.313	1.00	74.51
ATOM	1677	CD2	HIS	A	228	32.007	34.363	87.458	1.00	75.53
ATOM	1678	CE1	HIS	A	228	30.511	34.660	85.852	1.00	78.68
ATOM	1679	NE2	HIS	A	228	30.682	34.288	87.171	1.00	80.02
ATOM	1680	N	GLN	A	229	34.061	32.545	83.846	1.00	74.45
ATOM	1681	CA	GLN	A	229	33.306	31.659	82.963	1.00	81.06
ATOM	1682	C	GLN	A	229	33.569	30.149	83.028	1.00	85.59
ATOM	1683	O	GLN	A	229	33.123	29.427	82.135	1.00	86.52
ATOM	1684	CB	GLN	A	229	33.477	32.181	81.530	1.00	81.47
ATOM	1685	CG	GLN	A	229	33.002	33.631	81.335	1.00	81.55
ATOM	1686	CD	GLN	A	229	31.488	33.690	81.352	1.00	83.81
ATOM	1687	OE1	GLN	A	229	30.804	33.832	82.355	1.00	82.35
ATOM	1688	NE2	GLN	A	229	30.950	33.588	80.141	1.00	86.80
ATOM	1689	N	LYS	A	230	34.317	29.749	84.086	1.00	91.08
ATOM	1690	CA	LYS	A	230	34.965	28.444	84.325	1.00	95.45
ATOM	1691	CB	LYS	A	230	33.976	27.245	84.052	1.00	97.51
ATOM	1692	CG	LYS	A	230	34.256	26.053	83.073	1.00	98.30
ATOM	1693	CD	LYS	A	230	34.035	26.121	81.534	1.00	98.30
ATOM	1694	CE	LYS	A	230	34.810	27.172	80.713	1.00	100.00
ATOM	1695	NZ	LYS	A	230	36.244	27.239	81.067	1.00	100.00
ATOM	1696	C	LYS	A	230	36.409	28.279	83.743	1.00	97.06
ATOM	1697	OCT1	LYS	A	230	36.876	29.108	82.942	1.00	95.86
ATOM	1698	OCT2	LYS	A	230	37.052	27.241	83.957	1.00	99.89
ATOM	1935	S	SO4	S	231	22.561	63.872	89.148	1.00	45.29
ATOM	1936	O1	SO4	S	231	21.748	62.858	88.279	1.00	50.45
ATOM	1937	O2	SO4	S	231	21.648	64.707	90.036	1.00	51.74
ATOM	1938	O3	SO4	S	231	23.551	63.095	90.035	1.00	49.75
ATOM	1939	O4	SO4	S	231	23.260	64.912	88.285	1.00	44.08
ATOM	1	O	HOH	W	232	10.522	63.513	85.670	1.00	17.86
ATOM	2	O	HOH	W	233	34.116	63.633	80.578	1.00	20.45
ATOM	3	O	HOH	W	234	7.928	61.775	88.229	1.00	15.62
ATOM	4	O	HOH	W	235	10.374	64.545	82.597	1.00	14.58
ATOM	5	O	HOH	W	236	15.375	75.641	85.508	1.00	22.07
ATOM	6	O	HOH	W	237	20.773	44.507	86.785	1.00	18.67
ATOM	7	O	HOH	W	238	32.701	49.912	75.935	1.00	15.79
ATOM	8	O	HOH	W	239	21.979	72.096	84.493	1.00	19.08
ATOM	9	O	HOH	W	240	13.158	73.905	82.705	1.00	27.34
ATOM	10	O	HOH	W	241	14.358	71.880	73.410	1.00	26.83
ATOM	11	O	HOH	W	242	5.537	80.043	74.802	1.00	23.33
ATOM	12	O	HOH	W	243	36.136	62.604	78.407	1.00	23.19
ATOM	13	O	HOH	W	244	30.393	53.028	87.579	1.00	19.02
ATOM	14	O	HOH	W	245	28.532	49.107	93.252	1.00	21.32
ATOM	15	O	HOH	W	246	24.657	73.146	75.882	1.00	20.92
ATOM	16	O	HOH	W	247	10.080	55.567	81.848	1.00	33.80
ATOM	17	O	HOH	W	248	29.907	52.840	73.379	1.00	22.59
ATOM	18	O	HOH	W	249	38.583	48.054	74.575	1.00	24.10
ATOM	19	O	HOH	W	250	29.465	68.020	86.676	1.00	32.30
ATOM	20	O	HOH	W	251	12.847	73.680	85.460	1.00	40.76
ATOM	21	O	HOH	W	252	5.516	59.770	95.129	1.00	40.84
ATOM	22	O	HOH	W	253	42.504	47.354	77.319	1.00	30.77
ATOM	23	O	HOH	W	254	13.495	75.378	74.412	1.00	22.57
ATOM	24	O	HOH	W	255	17.100	76.564	77.737	1.00	30.00
ATOM	25	O	HOH	W	256	33.508	40.103	102.712	1.00	26.49

FIG. 42

ATOM	26	O	HOH	W	257	20.825	55.648	81.278	1.00	20.11
ATOM	27	O	HOH	W	258	19.730	61.701	89.970	1.00	23.10
ATOM	28	O	HOH	W	259	4.363	74.520	80.720	1.00	33.74
ATOM	29	O	HOH	W	260	31.490	42.656	98.480	1.00	34.19
ATOM	30	O	HOH	W	261	6.696	75.130	78.477	1.00	15.66
ATOM	31	O	HOH	W	262	10.667	67.023	75.103	1.00	38.86
ATOM	32	O	HOH	W	263	8.252	64.433	92.307	1.00	23.15
ATOM	33	O	HOH	W	264	41.924	51.223	74.247	1.00	30.19
ATOM	34	O	HOH	W	265	1.437	67.705	89.398	1.00	39.48
ATOM	35	O	HOH	W	266	4.055	66.946	91.467	1.00	29.22
ATOM	36	O	HOH	W	267	3.092	69.112	84.950	1.00	25.58
ATOM	37	O	HOH	W	268	9.537	59.065	79.795	1.00	30.90
ATOM	38	O	HOH	W	269	9.306	83.197	79.638	1.00	44.19
ATOM	39	O	HOH	W	270	34.786	41.166	75.522	1.00	32.98
ATOM	40	O	HOH	W	271	28.084	37.193	84.163	1.00	30.43
ATOM	41	O	HOH	W	272	40.742	49.227	76.024	1.00	21.82
ATOM	42	O	HOH	W	273	35.074	40.712	85.668	1.00	29.87
ATOM	43	O	HOH	W	274	30.318	45.526	96.384	1.00	35.57
ATOM	44	O	HOH	W	275	31.493	69.162	80.850	1.00	19.51
ATOM	45	O	HOH	W	276	42.914	61.700	76.016	1.00	28.69
ATOM	46	O	HOH	W	277	34.422	64.714	92.625	1.00	38.81
ATOM	47	O	HOH	W	278	13.405	78.374	80.916	1.00	25.22
ATOM	48	O	HOH	W	279	44.634	57.811	84.433	1.00	31.73
ATOM	49	O	HOH	W	280	44.303	60.992	82.740	1.00	28.14
ATOM	50	O	HOH	W	281	32.596	51.432	73.247	1.00	22.63
ATOM	51	O	HOH	W	282	22.182	40.126	75.125	1.00	27.50
ATOM	52	O	HOH	W	283	18.482	55.362	89.100	1.00	21.25
ATOM	53	O	HOH	W	284	36.960	42.360	74.192	1.00	28.88
ATOM	54	O	HOH	W	285	35.881	48.845	94.047	1.00	26.90
ATOM	55	O	HOH	W	286	26.212	59.698	94.760	1.00	23.37
ATOM	56	O	HOH	W	287	29.246	44.303	73.369	1.00	40.38
ATOM	57	O	HOH	W	288	27.356	35.947	80.422	1.00	31.74
ATOM	58	O	HOH	W	289	40.482	45.029	76.766	1.00	30.88
ATOM	59	O	HOH	W	290	24.864	58.724	91.112	1.00	25.30
ATOM	60	O	HOH	W	291	28.560	61.547	91.755	1.00	39.37
ATOM	61	O	HOH	W	292	27.888	63.113	90.252	1.00	40.28
ATOM	62	O	HOH	W	293	31.069	41.023	103.435	1.00	38.13
ATOM	63	O	HOH	W	294	5.144	47.860	86.978	1.00	37.63
ATOM	64	O	HOH	W	295	29.373	52.425	90.409	1.00	21.69
ATOM	65	O	HOH	W	296	41.571	51.401	87.864	1.00	31.72
ATOM	66	O	HOH	W	297	35.633	56.807	101.396	1.00	42.27
ATOM	67	O	HOH	W	298	35.257	40.157	78.063	1.00	30.17
ATOM	68	O	HOH	W	299	33.734	71.189	79.910	1.00	32.64
ATOM	69	O	HOH	W	300	17.659	69.593	75.158	1.00	46.73
ATOM	70	O	HOH	W	301	17.005	72.932	72.774	1.00	33.93
ATOM	71	O	HOH	W	302	15.769	48.059	85.107	1.00	24.21
ATOM	72	O	HOH	W	303	15.023	64.697	75.333	1.00	39.99
ATOM	73	O	HOH	W	304	13.546	67.305	74.469	1.00	38.11
ATOM	74	O	HOH	W	305	30.044	75.863	82.738	1.00	29.02
ATOM	75	O	HOH	W	306	5.253	66.383	98.323	1.00	61.09
ATOM	76	O	HOH	W	307	25.914	72.829	89.073	1.00	48.08
ATOM	77	O	HOH	W	308	38.474	67.620	76.050	1.00	32.88
ATOM	78	O	HOH	W	309	34.101	41.534	100.215	1.00	39.54
ATOM	79	O	HOH	W	310	29.974	37.419	76.650	1.00	39.99

FIG. 43

ATOM	80	O	HOH	W	311	17.829	44.406	81.773	1.00	29.29
ATOM	81	O	HOH	W	312	17.766	66.478	75.705	1.00	34.51
ATOM	82	O	HOH	W	313	35.983	70.225	78.152	1.00	38.85
ATOM	83	O	HOH	W	314	18.063	58.644	75.592	1.00	33.24
ATOM	84	O	HOH	W	315	17.740	45.824	75.692	1.00	31.29
ATOM	85	O	HOH	W	316	21.442	55.668	101.498	1.00	30.06
ATOM	86	O	HOH	W	317	30.660	37.639	105.501	1.00	46.34
ATOM	87	O	HOH	W	318	28.143	47.582	99.410	1.00	71.00
ATOM	88	O	HOH	W	319	11.398	65.394	76.821	1.00	34.86
ATOM	89	O	HOH	W	320	31.737	45.760	98.744	1.00	38.11
ATOM	90	O	HOH	W	321	16.084	45.559	87.137	1.00	43.68
ATOM	91	O	HOH	W	322	36.498	37.962	78.989	1.00	35.45
ATOM	92	O	HOH	W	323	41.868	42.172	76.980	1.00	56.04
ATOM	93	O	HOH	W	324	44.704	68.004	76.606	1.00	73.28
ATOM	94	O	HOH	W	325	30.214	44.935	101.119	1.00	28.63
ATOM	95	O	HOH	W	326	43.719	69.244	83.004	1.00	32.20
ATOM	96	O	HOH	W	327	7.992	54.768	93.490	1.00	36.05
ATOM	97	O	HOH	W	328	11.059	49.604	75.476	1.00	43.80
ATOM	98	O	HOH	W	329	17.730	37.202	79.516	1.00	44.41
ATOM	99	O	HOH	W	330	14.170	59.796	74.913	1.00	70.26
ATOM	100	O	HOH	W	331	28.648	70.326	88.645	1.00	34.35
ATOM	101	O	HOH	W	332	16.146	57.197	73.492	1.00	49.27
ATOM	102	O	HOH	W	333	11.086	52.502	82.116	1.00	39.47
ATOM	103	O	HOH	W	334	15.950	60.744	73.392	1.00	63.16
ATOM	104	O	HOH	W	335	23.809	74.443	89.142	1.00	63.73
ATOM	105	O	HOH	W	336	43.077	70.945	86.543	1.00	41.77
ATOM	106	O	HOH	W	337	44.625	68.578	85.466	1.00	42.53
ATOM	107	O	HOH	W	338	38.003	70.941	79.707	1.00	47.97
ATOM	108	O	HOH	W	339	42.635	39.826	86.317	1.00	39.90
ATOM	109	O	HOH	W	340	28.158	51.028	97.893	1.00	35.28
ATOM	110	O	HOH	W	341	34.562	57.666	98.193	1.00	56.42
ATOM	111	O	HOH	W	342	23.659	34.535	79.197	1.00	84.39
ATOM	112	O	HOH	W	343	10.337	58.458	76.704	1.00	45.85
ATOM	113	O	HOH	W	344	32.164	75.101	85.461	1.00	54.21
ATOM	114	O	HOH	W	345	32.930	38.410	86.586	1.00	43.15
ATOM	115	O	HOH	W	346	32.310	36.987	102.558	1.00	47.71
ATOM	116	O	HOH	W	347	11.163	49.101	82.634	1.00	84.37
ATOM	117	O	HOH	W	348	34.268	69.634	83.019	1.00	47.39
ATOM	118	O	HOH	W	349	31.352	37.085	89.579	1.00	74.88
ATOM	119	O	HOH	W	350	29.118	56.986	95.860	1.00	34.59
ATOM	120	O	HOH	W	351	1.634	70.786	81.659	1.00	41.89
ATOM	121	O	HOH	W	352	2.044	71.714	85.736	1.00	37.84
ATOM	122	O	HOH	W	353	16.219	75.511	74.471	1.00	44.53
ATOM	123	O	HOH	W	354	24.035	45.705	97.204	1.00	48.11
ATOM	124	O	HOH	W	355	17.939	77.382	82.853	1.00	65.65
ATOM	125	O	HOH	W	356	12.504	76.991	70.634	1.00	50.43
ATOM	126	O	HOH	W	357	16.951	78.295	74.889	1.00	47.02
ATOM	127	O	HOH	W	358	15.777	75.404	81.566	1.00	33.68
ATOM	128	O	HOH	W	359	37.401	72.376	82.831	1.00	50.52
ATOM	129	O	HOH	W	360	14.060	44.359	88.918	1.00	80.84
ATOM	130	O	HOH	W	361	32.619	76.123	75.757	1.00	42.84
ATOM	131	O	HOH	W	362	21.836	66.226	94.339	1.00	63.40
ATOM	132	O	HOH	W	363	16.011	46.526	82.837	1.00	38.42
ATOM	133	O	HOH	W	364	7.716	57.886	82.470	1.00	50.22

FIG. 44

ATOM	134	O	HOH	W	365	41.813	72.155	81.960	1.00	76.60
ATOM	135	O	HOH	W	366	5.810	63.614	94.440	1.00	41.72
ATOM	136	O	HOH	W	367	22.833	66.006	98.308	1.00	65.79
ATOM	137	O	HOH	W	368	21.384	36.791	76.692	1.00	59.29
ATOM	138	O	HOH	W	369	38.765	52.950	92.219	1.00	27.87
ATOM	139	O	HOH	W	370	46.430	68.991	81.609	1.00	70.52
ATOM	140	O	HOH	W	371	36.973	69.709	83.153	1.00	33.81
ATOM	141	O	HOH	W	372	22.238	43.716	92.825	1.00	44.49
ATOM	142	O	HOH	W	373	23.096	80.189	77.308	1.00	50.73
ATOM	143	O	HOH	W	374	2.790	53.932	81.478	1.00	50.22
ATOM	144	O	HOH	W	375	3.292	64.768	94.055	1.00	46.64
ATOM	145	O	HOH	W	376	26.937	79.257	75.755	1.00	47.21
ATOM	146	O	HOH	W	377	45.046	50.594	85.873	1.00	46.10
ATOM	147	O	HOH	W	378	24.988	68.312	90.158	1.00	39.03
ATOM	148	O	HOH	W	379	2.045	61.203	93.643	1.00	49.73
ATOM	149	O	HOH	W	380	44.273	56.110	87.700	1.00	46.74
ATOM	150	O	HOH	W	381	26.747	76.462	73.043	1.00	50.91
ATOM	151	O	HOH	W	382	40.545	70.889	76.918	1.00	68.80
ATOM	152	O	HOH	W	383	25.523	80.486	83.807	1.00	67.90
ATOM	153	O	HOH	W	384	40.972	36.296	87.372	1.00	66.49
ATOM	154	O	HOH	W	385	12.617	56.710	77.567	1.00	44.81
ATOM	155	O	HOH	W	386	44.460	48.054	74.082	1.00	41.02
ATOM	156	O	HOH	W	387	35.781	73.896	86.117	1.00	38.14
ATOM	157	O	HOH	W	388	21.625	80.398	81.815	1.00	47.96
ATOM	158	O	HOH	W	389	46.628	56.635	82.977	1.00	50.89
ATOM	159	O	HOH	W	390	12.308	51.573	78.083	1.00	64.92
ATOM	160	O	HOH	W	391	30.773	39.420	87.798	1.00	55.92
ATOM	161	O	HOH	W	392	26.088	65.110	89.923	1.00	44.80
ATOM	162	O	HOH	W	393	10.719	70.886	96.928	1.00	48.46
ATOM	163	O	HOH	W	394	12.474	47.243	84.457	1.00	53.08
ATOM	164	O	HOH	W	395	24.296	71.312	91.828	1.00	48.39
ATOM	165	O	HOH	W	396	6.459	50.108	83.133	1.00	57.82
ATOM	166	O	HOH	W	397	42.423	66.213	75.196	1.00	34.97
ATOM	167	O	HOH	W	398	29.045	53.518	101.769	1.00	46.59
ATOM	168	O	HOH	W	399	27.195	39.655	105.406	1.00	41.59
ATOM	169	O	HOH	W	400	6.834	56.385	96.211	1.00	45.81
ATOM	170	O	HOH	W	401	47.957	50.138	78.280	1.00	43.60
ATOM	171	O	HOH	W	402	23.330	36.461	72.787	1.00	54.41
ATOM	172	O	HOH	W	403	29.051	79.533	81.900	1.00	78.87
ATOM	173	O	HOH	W	404	46.670	55.026	74.340	1.00	68.61
ATOM	174	O	HOH	W	405	28.985	78.746	85.840	1.00	75.16
ATOM	175	O	HOH	W	406	32.117	68.589	73.365	1.00	42.10
ATOM	176	O	HOH	W	407	48.677	52.842	75.727	1.00	66.77
ATOM	177	O	HOH	W	408	29.185	36.245	72.017	1.00	75.24
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ATOM	186	O	HOH	W	417	30.230	76.830	74.341	1.00	71.09
ATOM	187	O	HOH	W	418	12.118	81.147	79.341	1.00	49.66

FIG. 45

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ATOM	190	O	HOH	W	421	10.822	64.227	102.313	1.00	81.32
ATOM	191	O	HOH	W	422	23.374	42.555	101.170	1.00	42.91
ATOM	192	O	HOH	W	423	20.016	59.713	74.793	1.00	38.45
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ATOM	206	O	HOH	W	437	9.462	82.415	76.470	1.00	48.44
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ATOM	209	O	HOH	W	440	18.118	43.497	86.455	1.00	46.86
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ATOM	215	O	HOH	W	446	33.012	71.334	90.213	1.00	53.98
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ATOM	221	O	HOH	W	452	23.011	77.967	75.363	1.00	64.04
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ATOM	225	O	HOH	W	456	16.108	40.093	81.126	1.00	98.28
ATOM	226	O	HOH	W	457	27.800	35.543	96.536	1.00	63.56
ATOM	227	O	HOH	W	458	5.859	51.318	95.801	1.00	68.96
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ATOM	230	O	HOH	W	461	13.943	46.268	81.680	1.00	56.20
ATOM	231	O	HOH	W	462	14.681	69.220	73.344	1.00	83.46
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ATOM	236	O	HOH	W	467	8.747	53.997	77.187	1.00	79.74
END										

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

MUTANT NUCLEOSIDE-5'-PHOSPHATE PRODUCING ENZYMES

the specification of which

☒ is attached hereto.

☐ was filed on ______________________ as

Application Serial No. ______________________

and amended on ______________________.

☒ was filed as PCT international application

Number PCT/JP 00/05973

on September 1, 2000,

and was amended under PCT Article 19

on ______________________ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed	
11-249545	Japan	September 3, 1999	☒ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	**Filing Date**	**Status (pending, patented, abandoned)**

And we (I) hereby appoint: Norman F. Oblon, Registration Number 24,618; Marvin J. Spivak, Registration Number 24,913; C. Irvin McClelland, Registration Number 21,124; Gregory J. Maier, Registration Number 25,599; Arthur I. Neustadt, Registration Number 24,854; Richard D. Kelly, Registration Number 27,757; James D. Hamilton, Registration Number 28,421; Eckhard H. Kuesters, Registration Number 28,870; Robert T. Pous, Registration Number 29,099; Charles L. Gholz, Registration Number 26,395; Vincent J. Sunderdick, Registration Number 29,004; William E. Beaumont, Registration Number 30,996; Steven B. Kelber, Registration Number 30,073; Robert F. Gnuse, Registration Number 27,295; Jean-Paul Lavalleye, Registration Number 31,451; Timothy R. Schwartz, Registration Number 32,171; Stephen G. Baxter, Registration Number 32,884; Martin M. Zoltick, Registration Number 35,745; Robert W. Hahl, Registration Number 33,893; Richard L. Treanor, Registration Number 36,379; Steven P. Weihrouch, Registration Number 32,829; John T. Goolkasian, Registration Number 26,142; Marc R. Labgold, Registration Number 34,651; William J. Healey, Registration Number 36,160; and Richard L. Chinn, Registration Number 34,305; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Date

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Date

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April 13, 2001

Date

NAME OF TWELFTH JOINT INVENTOR

Signature of Inventor

Date

NAME OF THIRTEENTH JOINT INVENTOR

Signature of Inventor

Date

SEQUENCE LISTING

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<141> 2000-09-01

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Ala Met Tyr Glu Lys Gly Arg Met Leu Arg Asn Thr Glu Arg Gly Lys
65 70 75 80
Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Gly Val Ala Thr Ala
85 90 95
Phe Ser Gly Ala Phe Gly Tyr Pro Ile Thr Glu Lys Asp Ser Pro Glu
100 105 110
Leu Tyr Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala

115 120 125
Thr Arg Ser Ala Lys Glu His Tyr Met Arg Ile Arg Pro Phe Ala Phe
130 135 140
Tyr Gly Thr Glu Thr Cys Asn Thr Lys Asp Gln Lys Lys Leu Ser Thr
145 150 155 160
Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly Trp Ala Thr Ala
165 170 175
Leu Val Leu Ala Glu Val Asn Pro Ala Asn Gln Asp Ala Ile Leu Glu
180 185 190
Arg Gly Tyr Gln Leu Gly Gln Ser Arg Val Ile Cys Gly Tyr His Trp
195 200 205
Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Ala Val Ala
210 215 220
Thr Leu His Ser Asp Pro Ala Phe Gln Ala Gln Leu Ala Lys Ala Lys
225 230 235 240
Gln Glu Phe Ala Gln Lys Ser Gln Lys
245

<210> 5
<211> 991
<212> DNA
<213> Salmonella typhimurium

<220>
<221> CDS
<222> (132)..(827)

<400> 5
cagtccggta tggacagacg ataatgccag gcgcagcgtc ctgctttttt acctgtatgt 60
tgaataacca ttgcaataaa tcattatagg attacatctg tttattattg cctgatccgg 120
agtgagtctt t atg aaa agt cgt tat tta gta ttt ttt cta cca ctg atc 170
Met Lys Ser Arg Tyr Leu Val Phe Phe Leu Pro Leu Ile
1 5 10
gta gct aaa tat aca tca gca gaa aca gtg caa ccc ttt cat tct cct 218
Val Ala Lys Tyr Thr Ser Ala Glu Thr Val Gln Pro Phe His Ser Pro
15 20 25
gaa gaa tca gtg aac agt cag ttc tac tta cca cca ccg cca ggt aat 266
Glu Glu Ser Val Asn Ser Gln Phe Tyr Leu Pro Pro Pro Pro Gly Asn
30 35 40 45
gat gat ccg gct tac cgc tat gat aag gag gct tat ttt aag ggc tat 314
Asp Asp Pro Ala Tyr Arg Tyr Asp Lys Glu Ala Tyr Phe Lys Gly Tyr
50 55 60
gcg ata aag ggt tcc ccg cga tgg aaa caa gct gct gag gat gca gat 362

Ala Ile Lys Gly Ser Pro Arg Trp Lys Gln Ala Ala Glu Asp Ala Asp
65 70 75
gta agc gtg gaa aat ata gcc aga ata ttc tcg cca gta gtg ggt gct 410
Val Ser Val Glu Asn Ile Ala Arg Ile Phe Ser Pro Val Val Gly Ala
80 85 90
aaa att aac ccc aaa gat acg cca gaa acc tgg aat atg tta aag aat 458
Lys Ile Asn Pro Lys Asp Thr Pro Glu Thr Trp Asn Met Leu Lys Asn
95 100 105
ctt ctg aca atg ggc ggc tac tac gct act gct tcg gca aaa aaa tat 506
Leu Leu Thr Met Gly Gly Tyr Tyr Ala Thr Ala Ser Ala Lys Lys Tyr
110 115 120 125
tat atg cgt acc cgc ccc ttt gtc tta ttt aat cat tcc acc tgc cgt 554
Tyr Met Arg Thr Arg Pro Phe Val Leu Phe Asn His Ser Thr Cys Arg
130 135 140
cct gaa gat gag aat act ttg cga aaa aat ggc tct tac cct tcc ggg 602
Pro Glu Asp Glu Asn Thr Leu Arg Lys Asn Gly Ser Tyr Pro Ser Gly
145 150 155
cat act gct tat ggt aca ctt ctg gca tta gta tta tcc gag gcc aga 650
His Thr Ala Tyr Gly Thr Leu Leu Ala Leu Val Leu Ser Glu Ala Arg
160 165 170
ccg gaa cgc gcg cag gag ctc gcc aga cgc gga tgg gag ttc ggg caa 698
Pro Glu Arg Ala Gln Glu Leu Ala Arg Arg Gly Trp Glu Phe Gly Gln
175 180 185
agc aga gtg ata tgc ggt gct cac tgg caa agc gat gtt gat gct ggc 746
Ser Arg Val Ile Cys Gly Ala His Trp Gln Ser Asp Val Asp Ala Gly
190 195 200 205
cgt tat gtg gga gca gta gag ttt gca aga ctg caa aca atc ccg gct 794
Arg Tyr Val Gly Ala Val Glu Phe Ala Arg Leu Gln Thr Ile Pro Ala
210 215 220
ttt cag aag tca ctg gca aaa tcc gtg agg agc tgaacgacaa aaataattta 847
Phe Gln Lys Ser Leu Ala Lys Ser Val Arg Ser
225 230
ttgagtaaag aagatcaccc caaacttaat tactgaaggt gaaagtcttc ccgcaaactg 907
gccacagcaa atgaaaggaa gtgcaactgc gtaggggcgg ccgggcgtgg agaatgcctt 967
tggtttcccc gattcgcatg aatt 991

<210> 6
<211> 232
<212> PRT
<213> Salmonella typhimurium

<400> 6
Met Lys Ser Arg Tyr Leu Val Phe Phe Leu Pro Leu Ile Val Ala Lys

1 5 10 15
Tyr Thr Ser Ala Glu Thr Val Gln Pro Phe His Ser Pro Glu Glu Ser
20 25 30
Val Asn Ser Gln Phe Tyr Leu Pro Pro Pro Pro Gly Asn Asp Asp Pro
35 40 45
Ala Tyr Arg Tyr Asp Lys Glu Ala Tyr Phe Lys Gly Tyr Ala Ile Lys
50 55 60
Gly Ser Pro Arg Trp Lys Gln Ala Ala Glu Asp Ala Asp Val Ser Val
65 70 75 80
Glu Asn Ile Ala Arg Ile Phe Ser Pro Val Val Gly Ala Lys Ile Asn
85 90 95
Pro Lys Asp Thr Pro Glu Thr Trp Asn Met Leu Lys Asn Leu Leu Thr
100 105 110
Met Gly Gly Tyr Tyr Ala Thr Ala Ser Ala Lys Lys Tyr Tyr Met Arg
115 120 125
Thr Arg Pro Phe Val Leu Phe Asn His Ser Thr Cys Arg Pro Glu Asp
130 135 140
Glu Asn Thr Leu Arg Lys Asn Gly Ser Tyr Pro Ser Gly His Thr Ala
145 150 155 160
Tyr Gly Thr Leu Leu Ala Leu Val Leu Ser Glu Ala Arg Pro Glu Arg
165 170 175
Ala Gln Glu Leu Ala Arg Arg Gly Trp Glu Phe Gly Gln Ser Arg Val
180 185 190
Ile Cys Gly Ala His Trp Gln Ser Asp Val Asp Ala Gly Arg Tyr Val
195 200 205
Gly Ala Val Glu Phe Ala Arg Leu Gln Thr Ile Pro Ala Phe Gln Lys
210 215 220
Ser Leu Ala Lys Ser Val Arg Ser
225 230

<210> 7
<211> 1335
<212> DNA
<213> Zymomonas mobilis

<220>
<221> CDS
<222> (317)..(1108)

<400> 7
gtgccttata tcacgggggg atcagtctgc ggcaattggt ggcatggcac gcgctacggc 60
acgccggaag gcttcatggt cgtcaaagtc gaaaagggta aagtcattcc gcattacgaa 120
agctatggct tccacacgat agacccgcgc aacacataat tgtcttatta tagccacatg 180

atatttttat attacaattt taaactaaaa ttaagaatta aattcttgaa ataaaggttt 240
ttttattaaa aggataggaa atgtcgtgaa atcggcattt tctatccata ttatataaca 300
agggaagact gacgac atg ata aaa gtc ccg cgg ttc atc tgt atg atc gcg 352
Met Ile Lys Val Pro Arg Phe Ile Cys Met Ile Ala
1 5 10

ctt aca tcc ggc gtt ctg gca agc ggc ctt tct caa agc gtt tca gct 400
Leu Thr Ser Gly Val Leu Ala Ser Gly Leu Ser Gln Ser Val Ser Ala
15 20 25

cat aca gaa aaa agt gaa ccc tcc tcg act tat cat ttc cac agc gat 448
His Thr Glu Lys Ser Glu Pro Ser Ser Thr Tyr His Phe His Ser Asp
30 35 40

ccc ctt ctt tac ctt gcg ccc cca ccc act tcc ggc agt cca tta cag 496
Pro Leu Leu Tyr Leu Ala Pro Pro Pro Thr Ser Gly Ser Pro Leu Gln
45 50 55 60

gcg cat gat gat caa acc ttt aac agc acc aga caa tta aaa ggt agc 544
Ala His Asp Asp Gln Thr Phe Asn Ser Thr Arg Gln Leu Lys Gly Ser
65 70 75

acg cgc tgg gca ttg gca act caa gat gcc gat ctt cat ctc gct tca 592
Thr Arg Trp Ala Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser
80 85 90

gtt ctc aaa gac tat gcc tgc gcc gca gga atg aat ctc gat att gcg 640
Val Leu Lys Asp Tyr Ala Cys Ala Ala Gly Met Asn Leu Asp Ile Ala
95 100 105

caa tta ccg cat ctt gcc aat ttg att aaa cgc gca ctt cgc acc gaa 688
Gln Leu Pro His Leu Ala Asn Leu Ile Lys Arg Ala Leu Arg Thr Glu
110 115 120

tat gac gat att ggc aga gcc aaa aat aac tgg aat cgc aaa cga cct 736
Tyr Asp Asp Ile Gly Arg Ala Lys Asn Asn Trp Asn Arg Lys Arg Pro
125 130 135 140

ttt gtg gat acc gat caa ccc atc tgc acg gaa aaa gat cgc gaa ggt 784
Phe Val Asp Thr Asp Gln Pro Ile Cys Thr Glu Lys Asp Arg Glu Gly
145 150 155

ctg gga aaa caa ggc tcc tat cct tca ggt cat acg act atc ggt tgg 832
Leu Gly Lys Gln Gly Ser Tyr Pro Ser Gly His Thr Thr Ile Gly Trp
160 165 170

agc gtt gcg ctc att ctg gct gaa ttg atc ccc gat cat gcg gcg aat 880
Ser Val Ala Leu Ile Leu Ala Glu Leu Ile Pro Asp His Ala Ala Asn
175 180 185

att ttg cag cgt ggc caa att ttt gga acc agc cgg att gtc tgc ggc 928
Ile Leu Gln Arg Gly Gln Ile Phe Gly Thr Ser Arg Ile Val Cys Gly
190 195 200

gcc cat tgg ttc agc gat gtg cag gca ggc tat atc atg gca tcg ggc 976
Ala His Trp Phe Ser Asp Val Gln Ala Gly Tyr Ile Met Ala Ser Gly

205 210 215 220
gaa att gca gct tta cat ggg gat gcc gat ttc cgc cga gat atg gaa 1024
Glu Ile Ala Ala Leu His Gly Asp Ala Asp Phe Arg Arg Asp Met Glu
225 230 235
tta gct cgg aaa gaa tta gaa aag gca cgc aca tca gcg cac acg cca 1072
Leu Ala Arg Lys Glu Leu Glu Lys Ala Arg Thr Ser Ala His Thr Pro
240 245 250
gac gat ctt cta tgc aag att gaa caa agc gct cgc taaattcaat 1118
Asp Asp Leu Leu Cys Lys Ile Glu Gln Ser Ala Arg
255 260
caagtattat ttcaacaagg ggaaagattg cttgctgtaa tttttggata tcaaacaggc 1178
gaaaaaatga aagagcgcac gctctttcaa aggcaattcg atttagtccg gtggcattct 1238
cacgccacaa accaaatcat aaataaccgc ctcttttccg ccagataact gcaaaattat 1298
agaataccga cagctggaat atcgtcactt ttcctag 1335

<210> 8
<211> 264
<212> PRT
<213> Zymomonas mobilis

<400> 8
Met Ile Lys Val Pro Arg Phe Ile Cys Met Ile Ala Leu Thr Ser Gly
1 5 10 15
Val Leu Ala Ser Gly Leu Ser Gln Ser Val Ser Ala His Thr Glu Lys
20 25 30
Ser Glu Pro Ser Ser Thr Tyr His Phe His Ser Asp Pro Leu Leu Tyr
35 40 45
Leu Ala Pro Pro Pro Thr Ser Gly Ser Pro Leu Gln Ala His Asp Asp
50 55 60
Gln Thr Phe Asn Ser Thr Arg Gln Leu Lys Gly Ser Thr Arg Trp Ala
65 70 75 80
Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser Val Leu Lys Asp
85 90 95
Tyr Ala Cys Ala Ala Gly Met Asn Leu Asp Ile Ala Gln Leu Pro His
100 105 110
Leu Ala Asn Leu Ile Lys Arg Ala Leu Arg Thr Glu Tyr Asp Asp Ile
115 120 125
Gly Arg Ala Lys Asn Asn Trp Asn Arg Lys Arg Pro Phe Val Asp Thr
130 135 140
Asp Gln Pro Ile Cys Thr Glu Lys Asp Arg Glu Gly Leu Gly Lys Gln
145 150 155 160
Gly Ser Tyr Pro Ser Gly His Thr Thr Ile Gly Trp Ser Val Ala Leu
165 170 175

Ile Leu Ala Glu Leu Ile Pro Asp His Ala Ala Asn Ile Leu Gln Arg
180 185 190
Gly Gln Ile Phe Gly Thr Ser Arg Ile Val Cys Gly Ala His Trp Phe
195 200 205
Ser Asp Val Gln Ala Gly Tyr Ile Met Ala Ser Gly Glu Ile Ala Ala
210 215 220
Leu His Gly Asp Ala Asp Phe Arg Arg Asp Met Glu Leu Ala Arg Lys
225 230 235 240
Glu Leu Glu Lys Ala Arg Thr Ser Ala His Thr Pro Asp Asp Leu Leu
245 250 255
Cys Lys Ile Glu Gln Ser Ala Arg
260

<210> 9
<211> 1650
<212> DNA
<213> Enterobacter aerogenes

<220>
<221> CDS
<222> (344)..(1087)

<220>
<221> mat_peptide
<222> (404)..(1087)

<220>
<221> sig_peptide
<222> (344)..(403)

<400> 9
gtcgacaaac ttcgcctgct cgctatgcag aatggtttcc agcactttag gggaaatttt 60
acaaccgcaa ccggctccgt ggctgtattg cgttaaacga atagcttgct cgctcatgga 120
catctcctgt cattgcaatc ccgctatggt agcgcccaaa cggcaaggtg ataagtgcga 180
cagtccgaaa tcgcgagtgg ttgctcatta agcagacaaa tatgcgtttt tgcgataccg 240
aacaattttt tcaatgtgat tttaactttt acttacagat gacaaaaatg tgactaaaaa 300
caaaaccatt gttctggaca tataacaccg taaggaaatg tag atg aaa aag cgc 355
Met Lys Lys Arg
-20
gtt ctc gcc ctc tgc ctc gcc agc ctg ttt tcc gtt aac gct ttc gcg 403
Val Leu Ala Leu Cys Leu Ala Ser Leu Phe Ser Val Asn Ala Phe Ala
-15 -10 -5 -1
ctg gtc cct gcc ggc aat gat gca acc acc aaa ccg gat ctc tat tat 451

Leu Val Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro Asp Leu Tyr Tyr
1 5 10 15
ctg aaa aat gca cag gcc atc gat agt ctg gcg ctg ttg ccg ccg ccg 499
Leu Lys Asn Ala Gln Ala Ile Asp Ser Leu Ala Leu Leu Pro Pro Pro
20 25 30
ccg gaa gtt ggc agc atc gca ttt tta aac gat cag gcg atg tat gag 547
Pro Glu Val Gly Ser Ile Ala Phe Leu Asn Asp Gln Ala Met Tyr Glu
35 40 45
aaa gga cgg ctg ttg cgc aat acc gaa cgt ggc aag cag gcg cag gca 595
Lys Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys Gln Ala Gln Ala
50 55 60
gat gct gac ctg gcc gcc ggc gac gtc gcg aat gcc ttc tcc agc gct 643
Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala Phe Ser Ser Ala
65 70 75 80
ttt ggt tcg ccc atc acc gaa aaa gac gcg ccg cag tta cat aag ctg 691
Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Gln Leu His Lys Leu
85 90 95
ctg aca aat atg att gag gat gcc ggc gat ctg gcc acc cgc agc gcg 739
Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala Thr Arg Ser Ala
100 105 110
aaa gag aaa tat atg cgc att cgc ccg ttt gcg ttc tac ggc gtt tca 787
Lys Glu Lys Tyr Met Arg Ile Arg Pro Phe Ala Phe Tyr Gly Val Ser
115 120 125
acc tgt aac act aaa gac cag gac aag ctg tcg aaa aac gga tct tac 835
Thr Cys Asn Thr Lys Asp Gln Asp Lys Leu Ser Lys Asn Gly Ser Tyr
130 135 140
cct tcc ggc cat acc tct acc ggt tgg gca acc gcg ctg gta ctg gcg 883
Pro Ser Gly His Thr Ser Thr Gly Trp Ala Thr Ala Leu Val Leu Ala
145 150 155 160
gag atc aat ccg cag cgg caa aac gaa att ctc aaa cgc ggc tat gaa 931
Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys Arg Gly Tyr Glu
165 170 175
ttg ggc gaa agc cgg gtt atc tgc ggc tat cat tgg cag agc gat gtc 979
Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr His Trp Gln Ser Asp Val
180 185 190
gat gcg gcg cgg ata gtc ggc tcg gcg gtg gtg gcg acc ctg cat acc 1027
Asp Ala Ala Arg Ile Val Gly Ser Ala Val Val Ala Thr Leu His Thr
195 200 205
aac ccg gcc ttc caa cag cag ttg cag aaa gca aag gat gaa ttc gcc 1075
Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys Asp Glu Phe Ala
210 215 220
aaa acg cag aag taacgtcatc gccgttgaac tcccggaggc ggcgcttaac 1127
Lys Thr Gln Lys

225
gcgccttctc cgggctacta aatcgcacag cgctgtagcc ccggtaagcg ccagcgccac 1187
cggggatttt gagatagcca gcaccagtag tttcagccag cgtgatgaat acattaacgg 1247
caggccgcat gagtcgtaga tactgttatc ggtttgcaac ttttttaagg tttttcccg 1307
gaggcggcgc gctgcgcctt ctccgggcta ctaaatcgca cagcgctgta gccccggtaa 1367
gcggcagcgc caccgggggt aacaagcgca gattcagaag cgcgtgacga acggcgcggt 1427
atccgggcgc gtaaacatgg ttgatgcttt taactgcggc gtgccaaggt agaggaaacc 1487
gacaattttg tcctgttcgc ggcagccaaa gccttcgcgg acaaccggac tctcggttaa 1547
cgcaccgata cgccagatac cgttatagcc ctgcgccact gcggccattt gcatcgccat 1607
caccgcacat cccgcggaca tctcctgttc ccacagcggt acc 1650

<210> 10
<211> 248
<212> PRT
<213> Enterobacter aerogenes

<400> 10
Met Lys Lys Arg Val Leu Ala Leu Cys Leu Ala Ser Leu Phe Ser Val
-20 -15 -10 -5
Asn Ala Phe Ala Leu Val Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro
-1 1 5 10
Asp Leu Tyr Tyr Leu Lys Asn Ala Gln Ala Ile Asp Ser Leu Ala Leu
15 20 25
Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Ala Phe Leu Asn Asp Gln
30 35 40
Ala Met Tyr Glu Lys Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys
45 50 55 60
Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala
65 70 75
Phe Ser Ser Ala Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Gln
80 85 90
Leu His Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
95 100 105
Thr Arg Ser Ala Lys Glu Lys Tyr Met Arg Ile Arg Pro Phe Ala Phe
110 115 120
Tyr Gly Val Ser Thr Cys Asn Thr Lys Asp Gln Asp Lys Leu Ser Lys
125 130 135 140
Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Thr Gly Trp Ala Thr Ala
145 150 155
Leu Val Leu Ala Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys
160 165 170
Arg Gly Tyr Glu Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr His Trp
175 180 185

Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Val Val Ala
    190   195   200
Thr Leu His Thr Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys
205   210   215   220
Asp Glu Phe Ala Lys Thr Gln Lys
                225

<210> 11
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 11
caaacctgag ctttggcgat gtggc 25

<210> 12
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 12
gtttggactc gaaaccgcta caccg 25

<210> 13
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino acid sequence around mutation

<400> 13
Asn Leu Ser Phe Gly Asp Val
  1   5

<210> 14

<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 14
caaacctgag ctacggcgat gtggc 25

<210> 15
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 15
gtttggactc gatgccgcta caccg 25

<210> 16
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino acid sequence around mutation

<400> 16
Asn Leu Ser Tyr Gly Asp Val
1 5

<210> 17
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 17

caaacctgag ctggggcgat gtggc 25

<210> 18
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 18
gtttggactc gaccccgcta caccg 25

<210> 19
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino
acid sequence around mutation

<400> 19
Asn Leu Ser Trp Gly Asp Val
1 5

<210> 20
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 20
caaacctgag cgacggcgat gtggc 25

<210> 21
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:primer

<400> 21
gtttggactc gctgccgcta caccg 25

<210> 22
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino
acid sequence around mutation

<400> 22
Asn Leu Ser Asp Gly Asp Val
1 5

<210> 23
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 23
caaacctgag cgttggcgat gtggc 25

<210> 24
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 24
gtttggactc gcaaccgcta caccg

<210> 25
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino acid sequence around mutation

<400> 25
Asn Leu Ser Val Gly Asp Val
  1   5

<210> 26
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 26
caaacctgag cgaaggcgat gtggc   25

<210> 27
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 27
gtttggactc gcttccgcta caccg   25

<210> 28
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino acid sequence around mutation

<400> 28
Asn Leu Ser Glu Gly Asp Val

1 5

<210> 29
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 29
caaacctgag catgggcgat gtggc 25

<210> 30
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 30
gtttggactc gtacccgcta caccg 25

<210> 31
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino acid sequence around mutation

<400> 31
Asn Leu Ser Met Gly Asp Val
1 5

<210> 32
<211> 25
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:primer

<400> 32
caaacctgag caccggcgat gtggc 25

<210> 33
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 33
gtttggactc gtggccgcta caccg 25

<210> 34
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino
acid sequence around mutation

<400> 34
Asn Leu Ser Thr Gly Asp Val
1 5

<210> 35
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 35
caaacctgag cctgggcgat gtggc 25

<210> 36
<211> 25
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 36
gtttggactc ggacccgcta caccg 25

<210> 37
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino
acid sequence around mutation

<400> 37
Asn Leu Ser Leu Gly Asp Val
1 5

<210> 38
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 38
caaacctgag ccgtggcgat gtggc 25

<210> 39
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 39
gtttggactc ggcaccgcta caccg 25

<210> 40
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino
acid sequence around mutation

<400> 40
Asn Leu Ser Arg Gly Asp Val
1 5

<210> 41
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 41
caaacctgag ccagggcgat gtggc 25

<210> 42
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:primer

<400> 42
gtttggactc ggtcccgcta caccg 25

<210> 43
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: partial amino
acid sequence around mutation

<400> 43
Asn Leu Ser Gln Gly Asp Val
1 5

<210> 44
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
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MUT300
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among acidic phosphatase family

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1 5 10

SEQUENCE LISTING

<110> ISHIKAWA, KOHKI

SUZUKI, EI-ICHIRO

GONDOH, KEIKO

SIMBA, NUBUHISA

MIHARA, YASUHIRO

KURAHASHI, OSAMU

KOUDA, TOHRU

SHIMAOKA, MEGUMI

KOZUTSUMI, RIE

ASANO, YASUHISA

<120> MUTANT NUCLEOSIDE-5'-PHOSPHATE PRODUCING ENZYMES

<130> 206523US0PCT

<140> 09/807,990

<141> 2000-09-01

<150> JP 11/249545

<151> 1999-09-03

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aagcaccctg tggcgctcat actggcaacc tgttgatatt aagcaacact cttcactcac     300

ggaattaaca cgcacagtaa aggtatacgc atg aaa aaa cgt gtt ctg gca gtt     354
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                                 1               5

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Cys Phe Ala Ala Leu Phe Ser Ser Gln Ala Leu Ala Leu Val Ala Thr
    10                  15                  20

ggc aac gac act acc acg aaa ccg gat ctc tac tac ctc aag aac agt      450
Gly Asn Asp Thr Thr Thr Lys Pro Asp Leu Tyr Tyr Leu Lys Asn Ser
25                  30                  35                  40

gaa gcc att aac agc ctg gcg ctg ttg ccg cca cca ccg gcg gtg ggc      498
Glu Ala Ile Asn Ser Leu Ala Leu Leu Pro Pro Pro Pro Ala Val Gly
                45                  50                  55

tcc att gcg ttt ctc aac gat cag gcc atg tat gaa cag ggg cgc ctg      546
Ser Ile Ala Phe Leu Asn Asp Gln Ala Met Tyr Glu Gln Gly Arg Leu
            60                  65                  70

ctg cgc aac acc gaa cgc ggt aag ctg gcg gcg gaa gat gca aac ctg      594
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75 80 85

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Ser Ser Gly Gly Val Ala Asn Ala Phe Ser Gly Ala Phe Gly Ser Pro
90 95 100

atc acc gaa aaa gac gcc ccg gcg ctg cat aaa tta ctg acc aat atg 690
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105 110 115 120

att gag gac gcc ggg gat ctg gcg acc cgc agc gcg aaa gat cac tat 738
Ile Glu Asp Ala Gly Asp Leu Ala Thr Arg Ser Ala Lys Asp His Tyr
125 130 135

atg cgc att cgt ccg ttc gcg ttt tat ggg gtc tct acc tgt aat acc 786
Met Arg Ile Arg Pro Phe Ala Phe Tyr Gly Val Ser Thr Cys Asn Thr
140 145 150

acc gag cag gac aaa ctg tcc aaa aat ggc tct tat ccg tcc ggg cat 834
Thr Glu Gln Asp Lys Leu Ser Lys Asn Gly Ser Tyr Pro Ser Gly His
155 160 165

acc tct atc ggc tgg gct act gcg ctg gtg ctg gca gag atc aac cct 882
Thr Ser Ile Gly Trp Ala Thr Ala Leu Val Leu Ala Glu Ile Asn Pro
170 175 180

cag cgc cag aac gag atc ctg aaa cgc ggt tat gag ctg ggc cag agc 930
Gln Arg Gln Asn Glu Ile Leu Lys Arg Gly Tyr Glu Leu Gly Gln Ser
185 190 195 200

cgg gtg att tgc ggc tac cac tgg cag agt gat gtg gat gcc gcg cgg 978
Arg Val Ile Cys Gly Tyr His Trp Gln Ser Asp Val Asp Ala Ala Arg
205 210 215

gta gtg gga tct gcc gtt gtg gcg acc ctg cat acc aac ccg gcg ttc 1026
Val Val Gly Ser Ala Val Val Ala Thr Leu His Thr Asn Pro Ala Phe
220 225 230

cag cag cag ttg cag aaa gcg aag gcc gaa ttc gcc cag cat cag aag 1074
Gln Gln Gln Leu Gln Lys Ala Lys Ala Glu Phe Ala Gln His Gln Lys
235 240 245

aaa taatcctgac taccgccttg ccttgcaggg cggtagtggt ttccactggc 1127
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Asp Leu Tyr Tyr Leu Lys Asn Ser Glu Ala Ile Asn Ser Leu Ala Leu
        35   40   45

Leu Pro Pro Pro Pro Ala Val Gly Ser Ile Ala Phe Leu Asn Asp Gln
    50   55   60

Ala Met Tyr Glu Gln Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys
65   70   75   80

Leu Ala Ala Glu Asp Ala Asn Leu Ser Ser Gly Gly Val Ala Asn Ala
                85   90   95

Phe Ser Gly Ala Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Ala
            100   105   110

Leu His Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
        115   120   125

Thr Arg Ser Ala Lys Asp His Tyr Met Arg Ile Arg Pro Phe Ala Phe
    130   135   140

Tyr Gly Val Ser Thr Cys Asn Thr Thr Glu Gln Asp Lys Leu Ser Lys
145   150   155   160

Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly Trp Ala Thr Ala
165 170 175

Leu Val Leu Ala Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys
180 185 190

Arg Gly Tyr Glu Leu Gly Gln Ser Arg Val Ile Cys Gly Tyr His Trp
195 200 205

Gln Ser Asp Val Asp Ala Ala Arg Val Val Gly Ser Ala Val Val Ala
210 215 220

Thr Leu His Thr Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys
225 230 235 240

Ala Glu Phe Ala Gln His Gln Lys Lys
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cttatttatc cgttcgttaa caaaagccat gctgtttctg tcaaattatc tgaaaatcat 180

catcaaaaat acttacctgt cttccgtctg tttcgtcaca ctttttgaa agagttaaca 240

tcaatttgca tctctccgcc ctacactggc agacaggttt ctgagtaata ctgttgtatc 300

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tgataaggag atgtc atg aag aag aat att atc gcc ggt tgt ctg ttc tca     351
                 Met Lys Lys Asn Ile Ile Ala Gly Cys Leu Phe Ser
                 1               5                   10

ctg ttt tcc ctt tcc gcg ctg gcc gcg atc ccg gcg ggc aac gat gcc      399
Leu Phe Ser Leu Ser Ala Leu Ala Ala Ile Pro Ala Gly Asn Asp Ala
        15                  20                  25

acc acc aag ccg gat tta tat tat ctg aaa aat gaa cag gct atc gac      447
Thr Thr Lys Pro Asp Leu Tyr Tyr Leu Lys Asn Glu Gln Ala Ile Asp
    30                  35                  40

agc ctg aaa ctg tta ccg cca ccg ccg gaa gtc ggc agt att cag ttt      495
Ser Leu Lys Leu Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Gln Phe
45                  50                  55                  60

tta aat gat cag gca atg tat gag aaa ggc cgt atg ctg cgc aat acc      543
Leu Asn Asp Gln Ala Met Tyr Glu Lys Gly Arg Met Leu Arg Asn Thr
                65                  70                  75

gag cgc gga aaa cag gca cag gca gat gct gac ctg gcc gca ggg ggt      591
Glu Arg Gly Lys Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Gly
            80                  85                  90

gtg gca acc gca ttt tca ggg gca ttc ggc tat ccg ata acc gaa aaa      639
Val Ala Thr Ala Phe Ser Gly Ala Phe Gly Tyr Pro Ile Thr Glu Lys
        95                  100                 105

gac tct ccg gag ctg tat aaa ctg ctg acc aat atg att gag gat gcc      687
Asp Ser Pro Glu Leu Tyr Lys Leu Leu Thr Asn Met Ile Glu Asp Ala
    110                 115                 120

ggt gat ctt gcc acc cgc tcc gcc aaa gaa cat tac atg cgc atc cgg      735
Gly Asp Leu Ala Thr Arg Ser Ala Lys Glu His Tyr Met Arg Ile Arg
125                 130                 135                 140

ccg ttt gcg ttt tac ggc aca gaa acc tgt aat acc aaa gat cag aaa      783
Pro Phe Ala Phe Tyr Gly Thr Glu Thr Cys Asn Thr Lys Asp Gln Lys
                145                 150                 155

aaa ctc tcc acc aac gga tct tac ccg tca ggt cat acg tct atc ggc      831
Lys Leu Ser Thr Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly
            160                 165                 170

tgg gca acc gca ctg gtg ctg gcg gaa gtg aac ccg gca aat cag gat      879
Trp Ala Thr Ala Leu Val Leu Ala Glu Val Asn Pro Ala Asn Gln Asp
        175                 180                 185

gcg att ctg gaa cgg ggt tat cag ctc gga cag agc cgg gtg att tgc      927
Ala Ile Leu Glu Arg Gly Tyr Gln Leu Gly Gln Ser Arg Val Ile Cys
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190 195 200

ggc tat cac tgg cag agt gat gtg gat gcc gcg cgg att gtc ggt tca 975
Gly Tyr His Trp Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser
205 210 215 220

gcc gct gtc gcg aca tta cat tcc gat ccg gca ttt cag gcg cag tta 1023
Ala Ala Val Ala Thr Leu His Ser Asp Pro Ala Phe Gln Ala Gln Leu
225 230 235

gcg aaa gcc aaa cag gaa ttt gca caa aaa tca cag aaa taaaagcagt 1072
Ala Lys Ala Lys Gln Glu Phe Ala Gln Lys Ser Gln Lys
240 245

gatatctggt cagggcagtg caatatctgc cctgaaatcc ctgtttattc ccacatccag 1132

cggtcttccc gatcccagcc ttttgttttc atgcagctgt agaaatagcg gttgcggctg 1192

tcttcattca catccatcac ataactttcc gttaccggtg tctgctcttt gtaggttttg 1252

ctgttaccgc agtcatcgtc ttttttgcag cgtttctcca catcccgcat cacactgcgc 1312

tgagcaactt catttttcac cggataaagc tt 1344

<210> 4

<211> 249

<212> PRT

<213> Morganella morganii

<400> 4

Met Lys Lys Asn Ile Ile Ala Gly Cys Leu Phe Ser Leu Phe Ser Leu
1 5 10 15

Ser Ala Leu Ala Ala Ile Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro
20 25 30

Asp Leu Tyr Tyr Leu Lys Asn Glu Gln Ala Ile Asp Ser Leu Lys Leu
35 40 45

Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Gln Phe Leu Asn Asp Gln
50 55 60

Ala Met Tyr Glu Lys Gly Arg Met Leu Arg Asn Thr Glu Arg Gly Lys
65 70 75 80

Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Gly Val Ala Thr Ala
85 90 95

Phe Ser Gly Ala Phe Gly Tyr Pro Ile Thr Glu Lys Asp Ser Pro Glu
100 105 110

Leu Tyr Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
115 120 125

Thr Arg Ser Ala Lys Glu His Tyr Met Arg Ile Arg Pro Phe Ala Phe
130 135 140

Tyr Gly Thr Glu Thr Cys Asn Thr Lys Asp Gln Lys Lys Leu Ser Thr
145 150 155 160

Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly Trp Ala Thr Ala
165 170 175

Leu Val Leu Ala Glu Val Asn Pro Ala Asn Gln Asp Ala Ile Leu Glu
180 185 190

Arg Gly Tyr Gln Leu Gly Gln Ser Arg Val Ile Cys Gly Tyr His Trp
195 200 205

Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Ala Val Ala
210 215 220

Thr Leu His Ser Asp Pro Ala Phe Gln Ala Gln Leu Ala Lys Ala Lys
225 230 235 240

Gln Glu Phe Ala Gln Lys Ser Gln Lys
245

<210> 5

<211> 991

<212> DNA

<213> Salmonella typhimurium

<220>

<221> CDS

<222> (132)..(827)

<223>

<400> 5
cagtccggta tggacagacg ataatgccag gcgcagcgtc ctgctttttt acctgtatgt 60

tgaataacca ttgcaataaa tcattatagg attacatctg tttattattg cctgatccgg 120

agtgagtctt t atg aaa agt cgt tat tta gta ttt ttt cta cca ctg atc 170
Met Lys Ser Arg Tyr Leu Val Phe Phe Leu Pro Leu Ile
1 5 10

gta gct aaa tat aca tca gca gaa aca gtg caa ccc ttt cat tct cct 218
Val Ala Lys Tyr Thr Ser Ala Glu Thr Val Gln Pro Phe His Ser Pro
15 20 25

gaa gaa tca gtg aac agt cag ttc tac tta cca cca ccg cca ggt aat 266
Glu Glu Ser Val Asn Ser Gln Phe Tyr Leu Pro Pro Pro Pro Gly Asn
30 35 40 45

gat gat ccg gct tac cgc tat gat aag gag gct tat ttt aag ggc tat 314
Asp Asp Pro Ala Tyr Arg Tyr Asp Lys Glu Ala Tyr Phe Lys Gly Tyr
50 55 60

gcg ata aag ggt tcc ccg cga tgg aaa caa gct gct gag gat gca gat 362
Ala Ile Lys Gly Ser Pro Arg Trp Lys Gln Ala Ala Glu Asp Ala Asp
65 70 75

gta agc gtg gaa aat ata gcc aga ata ttc tcg cca gta gtg ggt gct 410
Val Ser Val Glu Asn Ile Ala Arg Ile Phe Ser Pro Val Val Gly Ala
80 85 90

aaa att aac ccc aaa gat acg cca gaa acc tgg aat atg tta aag aat 458
Lys Ile Asn Pro Lys Asp Thr Pro Glu Thr Trp Asn Met Leu Lys Asn
95 100 105

ctt ctg aca atg ggc ggc tac tac gct act gct tcg gca aaa aaa tat 506
Leu Leu Thr Met Gly Gly Tyr Tyr Ala Thr Ala Ser Ala Lys Lys Tyr
110 115 120 125

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tat atg cgt acc cgc ccc ttt gtc tta ttt aat cat tcc acc tgc cgt        554
Tyr Met Arg Thr Arg Pro Phe Val Leu Phe Asn His Ser Thr Cys Arg
                130                 135                 140

cct gaa gat gag aat act ttg cga aaa aat ggc tct tac cct tcc ggg        602
Pro Glu Asp Glu Asn Thr Leu Arg Lys Asn Gly Ser Tyr Pro Ser Gly
            145                 150                 155

cat act gct tat ggt aca ctt ctg gca tta gta tta tcc gag gcc aga        650
His Thr Ala Tyr Gly Thr Leu Leu Ala Leu Val Leu Ser Glu Ala Arg
        160                 165                 170

ccg gaa cgc gcg cag gag ctc gcc aga cgc gga tgg gag ttc ggg caa        698
Pro Glu Arg Ala Gln Glu Leu Ala Arg Arg Gly Trp Glu Phe Gly Gln
    175                 180                 185

agc aga gtg ata tgc ggt gct cac tgg caa agc gat gtt gat gct ggc        746
Ser Arg Val Ile Cys Gly Ala His Trp Gln Ser Asp Val Asp Ala Gly
190                 195                 200                 205

cgt tat gtg gga gca gta gag ttt gca aga ctg caa aca atc ccg gct        794
Arg Tyr Val Gly Ala Val Glu Phe Ala Arg Leu Gln Thr Ile Pro Ala
                210                 215                 220

ttt cag aag tca ctg gca aaa tcc gtg agg agc tgaacgacaa aaataattta      847
Phe Gln Lys Ser Leu Ala Lys Ser Val Arg Ser
            225                 230

ttgagtaaag aagatcaccc caaacttaat tactgaaggt gaaagtcttc ccgcaaactg     907

gccacagcaa atgaaaggaa gtgcaactgc gtaggggcgg ccgggcgtgg agaatgcctt     967

tggtttcccc gattcgcatg aatt                                            991
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<210> 6

<211> 232

<212> PRT

<213> Salmonella typhimurium

<400> 6

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Met Lys Ser Arg Tyr Leu Val Phe Phe Leu Pro Leu Ile Val Ala Lys
1               5                   10                  15

Tyr Thr Ser Ala Glu Thr Val Gln Pro Phe His Ser Pro Glu Glu Ser
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20 25 30

Val Asn Ser Gln Phe Tyr Leu Pro Pro Pro Pro Gly Asn Asp Asp Pro
35 40 45

Ala Tyr Arg Tyr Asp Lys Glu Ala Tyr Phe Lys Gly Tyr Ala Ile Lys
50 55 60

Gly Ser Pro Arg Trp Lys Gln Ala Ala Glu Asp Ala Asp Val Ser Val
65 70 75 80

Glu Asn Ile Ala Arg Ile Phe Ser Pro Val Val Gly Ala Lys Ile Asn
85 90 95

Pro Lys Asp Thr Pro Glu Thr Trp Asn Met Leu Lys Asn Leu Leu Thr
100 105 110

Met Gly Gly Tyr Tyr Ala Thr Ala Ser Ala Lys Lys Tyr Tyr Met Arg
115 120 125

Thr Arg Pro Phe Val Leu Phe Asn His Ser Thr Cys Arg Pro Glu Asp
130 135 140

Glu Asn Thr Leu Arg Lys Asn Gly Ser Tyr Pro Ser Gly His Thr Ala
145 150 155 160

Tyr Gly Thr Leu Leu Ala Leu Val Leu Ser Glu Ala Arg Pro Glu Arg
165 170 175

Ala Gln Glu Leu Ala Arg Arg Gly Trp Glu Phe Gly Gln Ser Arg Val
180 185 190

Ile Cys Gly Ala His Trp Gln Ser Asp Val Asp Ala Gly Arg Tyr Val
195 200 205

Gly Ala Val Glu Phe Ala Arg Leu Gln Thr Ile Pro Ala Phe Gln Lys
210 215 220

Ser Leu Ala Lys Ser Val Arg Ser

225 230

<210> 7

<211> 1335

<212> DNA

<213> Zymomonas mobilis

<220>

<221> CDS

<222> (317)..(1108)

<223>

<400> 7

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gtgccttata tcacgggggg atcagtctgc ggcaattggt ggcatggcac gcgctacggc      60

acgccggaag gcttcatggt cgtcaaagtc gaaaagggta aagtcattcc gcattacgaa     120

agctatggct tccacacgat agacccgcgc aacacataat tgtcttatta tagccacatg     180

atattttat attacaattt taaactaaaa ttaagaatta aattcttgaa ataaaggttt      240

ttttattaaa aggataggaa atgtcgtgaa atcggcattt tctatccata ttatataaca     300

agggaagact gacgac atg ata aaa gtc ccg cgg ttc atc tgt atg atc gcg     352
                  Met Ile Lys Val Pro Arg Phe Ile Cys Met Ile Ala
                  1               5                   10

ctt aca tcc ggc gtt ctg gca agc ggc ctt tct caa agc gtt tca gct       400
Leu Thr Ser Gly Val Leu Ala Ser Gly Leu Ser Gln Ser Val Ser Ala
        15                  20                  25

cat aca gaa aaa agt gaa ccc tcc tcg act tat cat ttc cac agc gat       448
His Thr Glu Lys Ser Glu Pro Ser Ser Thr Tyr His Phe His Ser Asp
    30                  35                  40

ccc ctt ctt tac ctt gcg ccc cca ccc act tcc ggc agt cca tta cag       496
Pro Leu Leu Tyr Leu Ala Pro Pro Pro Thr Ser Gly Ser Pro Leu Gln
45                  50                  55                  60

gcg cat gat gat caa acc ttt aac agc acc aga caa tta aaa ggt agc       544
Ala His Asp Asp Gln Thr Phe Asn Ser Thr Arg Gln Leu Lys Gly Ser
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65 70 75

acg cgc tgg gca ttg gca act caa gat gcc gat ctt cat ctc gct tca 592
Thr Arg Trp Ala Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser
80 85 90

gtt ctc aaa gac tat gcc tgc gcc gca gga atg aat ctc gat att gcg 640
Val Leu Lys Asp Tyr Ala Cys Ala Ala Gly Met Asn Leu Asp Ile Ala
95 100 105

caa tta ccg cat ctt gcc aat ttg att aaa cgc gca ctt cgc acc gaa 688
Gln Leu Pro His Leu Ala Asn Leu Ile Lys Arg Ala Leu Arg Thr Glu
110 115 120

tat gac gat att ggc aga gcc aaa aat aac tgg aat cgc aaa cga cct 736
Tyr Asp Asp Ile Gly Arg Ala Lys Asn Asn Trp Asn Arg Lys Arg Pro
125 130 135 140

ttt gtg gat acc gat caa ccc atc tgc acg gaa aaa gat cgc gaa ggt 784
Phe Val Asp Thr Asp Gln Pro Ile Cys Thr Glu Lys Asp Arg Glu Gly
145 150 155

ctg gga aaa caa ggc tcc tat cct tca ggt cat acg act atc ggt tgg 832
Leu Gly Lys Gln Gly Ser Tyr Pro Ser Gly His Thr Thr Ile Gly Trp
160 165 170

agc gtt gcg ctc att ctg gct gaa ttg atc ccc gat cat gcg gcg aat 880
Ser Val Ala Leu Ile Leu Ala Glu Leu Ile Pro Asp His Ala Ala Asn
175 180 185

att ttg cag cgt ggc caa att ttt gga acc agc cgg att gtc tgc ggc 928
Ile Leu Gln Arg Gly Gln Ile Phe Gly Thr Ser Arg Ile Val Cys Gly
190 195 200

gcc cat tgg ttc agc gat gtg cag gca ggc tat atc atg gca tcg ggc 976
Ala His Trp Phe Ser Asp Val Gln Ala Gly Tyr Ile Met Ala Ser Gly
205 210 215 220

gaa att gca gct tta cat ggg gat gcc gat ttc cgc cga gat atg gaa 1024
Glu Ile Ala Ala Leu His Gly Asp Ala Asp Phe Arg Arg Asp Met Glu
225 230 235

tta gct cgg aaa gaa tta gaa aag gca cgc aca tca gcg cac acg cca 1072
Leu Ala Arg Lys Glu Leu Glu Lys Ala Arg Thr Ser Ala His Thr Pro
240 245 250

gac gat ctt cta tgc aag att gaa caa agc gct cgc taaattcaat 1118
Asp Asp Leu Leu Cys Lys Ile Glu Gln Ser Ala Arg
255 260

caagtattat ttcaacaagg ggaaagattg cttgctgtaa tttttggata tcaaacaggc 1178

gaaaaaatga aagagcgcac gctctttcaa aggcaattcg atttagtccg gtggcattct 1238

cacgccacaa accaaatcat aaataaccgc ctcttttccg ccagataact gcaaaattat 1298

agaataccga cagctggaat atcgtcactt ttcctag 1335

<210> 8

<211> 264

<212> PRT

<213> Zymomonas mobilis

<400> 8

Met Ile Lys Val Pro Arg Phe Ile Cys Met Ile Ala Leu Thr Ser Gly
1   5   10   15

Val Leu Ala Ser Gly Leu Ser Gln Ser Val Ser Ala His Thr Glu Lys
            20   25   30

Ser Glu Pro Ser Ser Thr Tyr His Phe His Ser Asp Pro Leu Leu Tyr
        35   40   45

Leu Ala Pro Pro Pro Thr Ser Gly Ser Pro Leu Gln Ala His Asp Asp
    50   55   60

Gln Thr Phe Asn Ser Thr Arg Gln Leu Lys Gly Ser Thr Arg Trp Ala
65   70   75   80

Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser Val Leu Lys Asp
                85   90   95

Tyr Ala Cys Ala Ala Gly Met Asn Leu Asp Ile Ala Gln Leu Pro His
            100   105   110

Leu Ala Asn Leu Ile Lys Arg Ala Leu Arg Thr Glu Tyr Asp Asp Ile
        115   120   125

Gly Arg Ala Lys Asn Asn Trp Asn Arg Lys Arg Pro Phe Val Asp Thr

130 135 140

Asp Gln Pro Ile Cys Thr Glu Lys Asp Arg Glu Gly Leu Gly Lys Gln
145 150 155 160

Gly Ser Tyr Pro Ser Gly His Thr Thr Ile Gly Trp Ser Val Ala Leu
165 170 175

Ile Leu Ala Glu Leu Ile Pro Asp His Ala Ala Asn Ile Leu Gln Arg
180 185 190

Gly Gln Ile Phe Gly Thr Ser Arg Ile Val Cys Gly Ala His Trp Phe
195 200 205

Ser Asp Val Gln Ala Gly Tyr Ile Met Ala Ser Gly Glu Ile Ala Ala
210 215 220

Leu His Gly Asp Ala Asp Phe Arg Arg Asp Met Glu Leu Ala Arg Lys
225 230 235 240

Glu Leu Glu Lys Ala Arg Thr Ser Ala His Thr Pro Asp Asp Leu Leu
245 250 255

Cys Lys Ile Glu Gln Ser Ala Arg
260

<210> 9

<211> 1650

<212> DNA

<213> Enterobacter aerogenes

<220>

<221> CDS

<222> (344)..(1087)

<223>

<220>

<221> mat_peptide

<222> (404)..()

<223>

<220>

<221> sig_peptide

<222> (344)..(403)

<223>

<400> 9

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gtcgacaaac ttcgcctgct cgctatgcag aatggtttcc agcactttag gggaaatttt      60

acaaccgcaa ccggctccgt ggctgtattg cgttaaacga atagcttgct cgctcatgga     120

catctcctgt cattgcaatc ccgctatggt agcgcccaaa cggcaaggtg ataagtgcga     180

cagtccgaaa tcgcgagtgg ttgctcatta agcagacaaa tatgcgtttt tgcgataccg     240

aacaattttt tcaatgtgat tttaactttt acttacagat gacaaaaatg tgactaaaaa     300

caaaaccatt gttctggaca tataacaccg taaggaaatg tag atg aaa aag cgc       355
                                                Met Lys Lys Arg
                                                -20

gtt ctc gcc ctc tgc ctc gcc agc ctg ttt tcc gtt aac gct ttc gcg       403
Val Leu Ala Leu Cys Leu Ala Ser Leu Phe Ser Val Asn Ala Phe Ala
    -15                 -10                 -5                  -1

ctg gtc cct gcc ggc aat gat gca acc acc aaa ccg gat ctc tat tat       451
Leu Val Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro Asp Leu Tyr Tyr
1               5                   10                  15

ctg aaa aat gca cag gcc atc gat agt ctg gcg ctg ttg ccg ccg ccg       499
Leu Lys Asn Ala Gln Ala Ile Asp Ser Leu Ala Leu Leu Pro Pro Pro
            20                  25                  30

ccg gaa gtt ggc agc atc gca ttt tta aac gat cag gcg atg tat gag       547
Pro Glu Val Gly Ser Ile Ala Phe Leu Asn Asp Gln Ala Met Tyr Glu
        35                  40                  45
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aaa gga cgg ctg ttg cgc aat acc gaa cgt ggc aag cag gcg cag gca 595
Lys Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys Gln Ala Gln Ala
50 55 60

gat gct gac ctg gcc gcc ggc gac gtc gcg aat gcc ttc tcc agc gct 643
Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala Phe Ser Ser Ala
65 70 75 80

ttt ggt tcg ccc atc acc gaa aaa gac gcg ccg cag tta cat aag ctg 691
Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Gln Leu His Lys Leu
85 90 95

ctg aca aat atg att gag gat gcc ggc gat ctg gcc acc cgc agc gcg 739
Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala Thr Arg Ser Ala
100 105 110

aaa gag aaa tat atg cgc att cgc ccg ttt gcg ttc tac ggc gtt tca 787
Lys Glu Lys Tyr Met Arg Ile Arg Pro Phe Ala Phe Tyr Gly Val Ser
115 120 125

acc tgt aac act aaa gac cag gac aag ctg tcg aaa aac gga tct tac 835
Thr Cys Asn Thr Lys Asp Gln Asp Lys Leu Ser Lys Asn Gly Ser Tyr
130 135 140

cct tcc ggc cat acc tct acc ggt tgg gca acc gcg ctg gta ctg gcg 883
Pro Ser Gly His Thr Ser Thr Gly Trp Ala Thr Ala Leu Val Leu Ala
145 150 155 160

gag atc aat ccg cag cgg caa aac gaa att ctc aaa cgc ggc tat gaa 931
Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys Arg Gly Tyr Glu
165 170 175

ttg ggc gaa agc cgg gtt atc tgc ggc tat cat tgg cag agc gat gtc 979
Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr His Trp Gln Ser Asp Val
180 185 190

gat gcg gcg cgg ata gtc ggc tcg gcg gtg gtg gcg acc ctg cat acc 1027
Asp Ala Ala Arg Ile Val Gly Ser Ala Val Val Ala Thr Leu His Thr
195 200 205

aac ccg gcc ttc caa cag cag ttg cag aaa gca aag gat gaa ttc gcc 1075
Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys Asp Glu Phe Ala
210 215 220

aaa acg cag aag taacgtcatc gccgttgaac tcccggaggc ggcgcttaac 1127
Lys Thr Gln Lys
225

gcgccttctc cgggctacta aatcgcacag cgctgtagcc ccggtaagcg ccagcgccac 1187

cggggatttt gagatagcca gcaccagtag tttcagccag cgtgatgaat acattaacgg 1247

caggccgcat gagtcgtaga tactgttatc ggtttgcaac ttttttaagg tttttcccg 1307

gaggcggcgc gctgcgcctt ctccgggcta ctaaatcgca cagcgctgta gccccggtaa 1367

gcggcagcgc caccgggggt aacaagcgca gattcagaag cgcgtgacga acggcgcggt 1427

atccgggcgc gtaaacatgg ttgatgcttt taactgcggc gtgccaaggt agaggaaacc 1487

gacaattttg tcctgttcgc ggcagccaaa gccttcgcgg acaaccggac tctcggttaa 1547

cgcaccgata cgccagatac cgttatagcc ctgcgccact gcggccattt gcatcgccat 1607

caccgcacat cccgcggaca tctcctgttc ccacagcggt acc 1650

<210> 10

<211> 248

<212> PRT

<213> Enterobacter aerogenes

<400> 10

Met Lys Lys Arg Val Leu Ala Leu Cys Leu Ala Ser Leu Phe Ser Val
-20 -15 -10 -5

Asn Ala Phe Ala Leu Val Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro
-1 1 5 10

Asp Leu Tyr Tyr Leu Lys Asn Ala Gln Ala Ile Asp Ser Leu Ala Leu
15 20 25

Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Ala Phe Leu Asn Asp Gln
30 35 40

Ala Met Tyr Glu Lys Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys
45 50 55 60

Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala
65 70 75

Phe Ser Ser Ala Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Gln

80 85 90

Leu His Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
95 100 105

Thr Arg Ser Ala Lys Glu Lys Tyr Met Arg Ile Arg Pro Phe Ala Phe
110 115 120

Tyr Gly Val Ser Thr Cys Asn Thr Lys Asp Gln Asp Lys Leu Ser Lys
125 130 135 140

Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Thr Gly Trp Ala Thr Ala
145 150 155

Leu Val Leu Ala Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys
160 165 170

Arg Gly Tyr Glu Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr His Trp
175 180 185

Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Val Val Ala
190 195 200

Thr Leu His Thr Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys
205 210 215 220

Asp Glu Phe Ala Lys Thr Gln Lys
225

<210> 11

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 11
caaacctgag ctttggcgat gtggc 25

<210> 12

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 12
gtttggactc gaaaccgcta caccg 25

<210> 13

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Internal peptide of Escherichia blattae acid phosphatase with mut
ation

<400> 13

Asn Leu Ser Phe Gly Asp Val
1   5

<210> 14

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 14
caaacctgag ctacggcgat gtggc 25

<210> 15

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 15
gtttggactc gatgccgcta caccg 25

<210> 16

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Internal peptide of Escherichia blattae acid phosphatase with mut
ation

<400> 16

Asn Leu Ser Tyr Gly Asp Val
1 5

<210> 17

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 17
caaacctgag ctggggcgat gtggc   25

<210> 18

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 18
gtttggactc gaccccgcta caccg   25

<210> 19

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Internal peptide of Escherichia blattae acid phosphatase with mut
ation

<400> 19

Asn Leu Ser Trp Gly Asp Val
1   5

<210> 20

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 20
caaacctgag cgacggcgat gtggc   25

<210> 21

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 21
gtttggactc gctgccgcta caccg   25

<210> 22

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Internal peptide of Escherichia blattae acid phosphatase with mut
       ation

<400> 22

Asn Leu Ser Asp Gly Asp Val

1   5

<210> 23

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Sythetic DNA

<400> 23
caaacctgag cgttggcgat gtggc   25

<210> 24

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 24
gtttggactc gcaaccgcta caccg   25

<210> 25

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Internal peptide of Escherichia blattae acid phosphatase with mut

ation

<400> 25

Asn Leu Ser Val Gly Asp Val
1   5

<210> 26

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 26
caaacctgag cgaaggcgat gtggc 25

<210> 27

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

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